CLINICAL—LIVER

Simple Noninvasive Systems Predict Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease

PAUL ANGULO,[1] ELISABETTA BUGIANESI,[2] EINAR S. BJORNSSON,[3] PHUNCHAI CHARATCHAROENWITTHAYA,[4] PETER R. MILLS,[5] FRANCISCO BARRERA,[6] SVANHILDUR HAFLIDADOTTIR,[3] CHRISTOPHER P. DAY,[7,§] and JACOB GEORGE[6,§]

[1]Division of Digestive Diseases and Nutrition, University of Kentucky Medical Center, Lexington, Kentucky; [2]Division of Gastroenterology and Hepatology, Department of Medical Sciences, University of Torino, Torino, Italy; [3]Section of Gastroenterology and Hepatology, National University Hospital, Reykjavik, Iceland; [4]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Gartnavel General Hospital, Glasgow, UK; [6]Storr Liver Unit, Westmead Millennium Institute, University of Sydney and Department of Gastroenterology and Hepatology, Westmead Hospital, Westmead, New South Wales, Australia; and [7]Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle, United Kingdom

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BACKGROUND & AIMS: Some patients with nonalcoholic fatty liver disease (NAFLD) develop liver-related complications and have higher mortality than other patients with NAFLD. We determined the accuracy of simple, noninvasive scoring systems in identification of patients at increased risk for liver-related complications or death. **METHODS:** We performed a retrospective, international, multicenter cohort study of 320 patients diagnosed with NAFLD, based on liver biopsy analysis through 2002 and followed through 2011. Patients were assigned to mild-, intermediate-, or high-risk groups based on cutoff values for 2 of the following: NAFLD fibrosis score, aspartate aminotransferase/platelet ratio index, FIB-4 score, and BARD score. Outcomes included liver-related complications and death or liver transplantation. We used multivariate Cox proportional hazard regression analysis to adjust for relevant variables and calculate adjusted hazard ratios (aHRs). **RESULTS:** During a median follow-up period of 104.8 months (range, 3–317 months), 14% of patients developed liver-related events and 13% died or underwent liver transplantation. The aHRs for liver-related events in the intermediate-risk and high-risk groups, compared with the low-risk group, were 7.7 (95% confidence interval [CI]: 1.4–42.7) and 34.2 (95% CI: 6.5–180.1), respectively, based on NAFLD fibrosis score; 8.8 (95% CI: 1.1–67.3) and 20.9 (95% CI: 2.6–165.3) based on the aspartate aminotransferase/platelet ratio index; and 6.2 (95% CI: 1.4–27.2) and 6.6 (95% CI: 1.4–31.1) based on the BARD score. The aHRs for death or liver transplantation in the intermediate-risk and high-risk groups compared with the low-risk group were 4.2 (95% CI: 1.3–13.8) and 9.8 (95% CI: 2.7–35.3), respectively, based on the NAFLD fibrosis scores. Based on aspartate aminotransferase/platelet ratio index and FIB-4 score, only the high-risk group had a greater risk of death or liver transplantation (aHR = 3.1; 95% CI: 1.1–8.4 and aHR = 6.6; 95% CI: 2.3–20.4, respectively). **CONCLUSIONS: Simple noninvasive scoring systems help identify patients with NAFLD who are at increased risk for liver-related complications or death. NAFLD fibrosis score appears to be the best indicator of patients at risk, based on HRs. The results of this study require external validation.**

Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of liver pathology ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), the latter characterized by steatosis plus features of cellular injury, such as inflammation and hepatocyte ballooning.[1] Some patients with NAFLD develop liver fibrosis, with a proportion progressing to cirrhosis and its complications of liver failure, portal hypertension, and hepatocellular carcinoma (HCC).[2–4] Currently, cirrhotic-stage NAFLD represents the third[5] or fourth[6] most common indication for liver transplantation in the United States, and the second most common indication for liver transplantation in large transplantation centers.[7] In addition, the prevalence of NAFLD-related cirrhosis has markedly increased in recent years as the underlying liver disease among patients transplanted for HCC in the United States.[8] These data reflect the high prevalence of NAFLD in the general population, putting a substantial proportion of individuals at risk for NAFLD-associated morbidity and mortality.[9]

The long-term prognosis for individuals with NAFLD is not the same across the spectrum of the disease. Steatosis not associated with cellular injury or fibrosis

§Authors share co-senior authorship.

Abbreviations used in this paper: aHR, adjusted hazard ratio; ALT, alanine aminotransferase; APRI, AST/platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NAFLD-FS, NAFLD fibrosis score; NASH, nonalcoholic steatohepatitis; ROC, receiver operating characteristic.

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follows a relatively benign clinical course, with an overall mortality similar to the general population of the same age and sex.[10,11] For instance, <1% of patients with simple steatosis progressed to cirrhosis or died from liver-related complication after a mean follow-up of 15 years in a pooled analysis of several reported series.[12] However, patients with NASH, particularly those with increased fibrosis, have a worse prognosis as compared with an age- and sex-matched population.[11] The prevalence of cirrhosis and death related to liver complications is about 11% and 7%, respectively, in patients with NASH during the first 15 years of follow-up.[12] It has become clear that a subgroup of patients with NAFLD are at a higher risk for development of liver-related complications and death from liver-related causes. Unfortunately, other than presenting with overt cirrhosis or having a liver biopsy demonstrating advanced liver fibrosis, there is no accurate way to predict which subgroup of patients with NAFLD are at a higher risk for development of adverse long-term outcomes, including liver-related complications, liver transplantation, or death.

Several noninvasive scoring systems composed of routinely measured clinical and laboratory variables have been proposed to distinguish between patients with NAFLD with and without advanced liver fibrosis, including the NAFLD fibrosis score (NAFLD-FS),[13] the AST/platelet ratio index (APRI),[14] the FIB-4 score,[15] and the BARD score.[16] Most have been extensively validated for their accuracy in distinguishing between NAFLD patients with and without advanced fibrosis.[17–19] It remains unknown, however, whether these scores can be used to identify the subgroup of patients with NAFLD who are at a higher risk for liver-related morbidity and mortality. We sought to determine the accuracy of these 4 scores in predicting the long-term outcomes of patients with NAFLD, including liver-related complications, transplantation, or overall mortality.

Patients and Methods

This was a retrospective, international, multicenter cohort study of 320 patients with well-characterized and liver biopsy–confirmed NAFLD. They were untreated, consecutively biopsied patients that met the eligibility criteria as described here, and were recruited before 2002 from the following medical centers: University of Kentucky Medical Center, Lexington, KY; Westmead Hospital, Sydney Australia; Newcastle Hospitals National Health Service Foundation Trust in Newcastle-upon-Tyne, UK; National University Hospital, Reykjavik Iceland; Siriraj Hospital, Mahidol University, Bangkok, Thailand; Gartnavel General Hospital, Glasgow, UK; and Division of Gastroenterology and Hepatology University of Torino, Torino, Italy. The year 2002 was chosen in order to have up to a decade of follow-up for the last patient recruited into the study. The first subject included underwent a liver biopsy in 1984. Patients were retrospectively identified by reviewing the pathology database at each center of subjects with the pathology diagnosis of steatosis, steatohepatitis, or fatty liver. After an extensive review of the patients' medical records, only those with an unequivocal diagnosis of NAFLD were included in the analysis. The liver biopsy was performed to confirm the diagnosis of NAFLD after appropriate exclusion of liver disease of other etiology, such as alcohol-induced or drug-induced liver disease, autoimmune or viral hepatitis, and cholestatic or metabolic/genetic liver disease. These other liver diseases were excluded using specific clinical, laboratory, radiographic, and/or histological criteria. Serology for viral hepatitis B and C was investigated in all subjects and all tested negative. Serology for hepatitis C virus was investigated either before the liver biopsy in those biopsied after 1991 when serology for hepatitis C virus became available, or on subsequent visits for those biopsied before hepatitis C virus testing was available. All patients had a negative history of alcohol abuse, as indicated by a weekly ethanol consumption of <140 g in women and <210 g in men. History of alcohol consumption was specifically investigated by interviewing the patients and, in many cases, by also interviewing close relatives. No subjects underwent bariatric surgery before or during the study period, and none received treatment with vitamin E or a glitazone.

Extensive clinical and laboratory data were collected at the time the liver biopsy was performed. A complete medical history and physical examination were completed in all patients. The ethnicity (Hispanic or Latino, and not Hispanic or Latino) and race (white, Asian, black or African American, American Indian/Alaska native, Native Hawaiian or other Pacific Islander) of the patients were determined based on the categories proposed by the US Department of Health and Human Services Public Health Service.[20] Body mass index (BMI) was calculated using the formula: weight (in kilograms)/height (in meters^2). Waist circumference (to the nearest half centimeter) was measured at the midpoint between the lower border of the rib cage and the iliac crest. Laboratory evaluation included routine liver biochemistry (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels, total bilirubin, albumin, alkaline phosphatase, and γ-glutamyl transpeptidase); complete blood count; total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; fasting glucose; serum ferritin; transferrin saturation; viral serology for hepatitis B and C infection; autoantibodies; α1 antitrypsin levels and phenotype; and ceruloplasmin levels. Components of the metabolic syndrome[21] were recorded, including central obesity (waist circumference >102 cm for men and >88 cm for women; or ≥90 cm in Asian men and ≥80 cm in Asian women), obesity (BMI ≥30 or ≥25 in Asians) and overweight (BMI 25–29.9 or 23–24.9 in Asians), hyperglycemia (fasting blood glucose ≥6.1 mmol/L or previously diagnosed type 2 diabetes), hypertriglyceridemia (triglycerides ≥1.7 mmol/L or under treatment for this lipid abnormality), hypertension (blood pressure ≥130/≥85 mm Hg or treatment of previously diagnosed hypertension), and low high-density lipoprotein cholesterol (<1.04 mmol/L in men or <1.3 mmol/L in women). The presence of diabetes mellitus (fasting glucose ≥7.0 mmol/L or treatment with antidiabetic drugs) was also recorded. Data on the use of statins during the study period were collected from review of medical records.

Four validated noninvasive scoring systems that were originally created to distinguish between patients with and without advanced (stage 3–4) liver fibrosis were calculated using the original reported formulas.[13–16] They were the NAFLD-FS formula: $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI $+ 1.13 \times$ hyperglycemia or diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dL); the APRI formula: AST ($\times$ upper limit of normal) / platelet(10^9/L)] $\times$ 100; the FIB-4 score formula: [age (years) $\times$ AST (U/L) / platelet(10^9/L) $\times \sqrt{}$ALT (U/L)]; the BARD score, scale 0–4: BMI

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