The Natural History of Nonalcoholic Fatty Liver Disease With Advanced Fibrosis or Cirrhosis: An International Collaborative Study

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Information on the long-term prognosis of nonalcoholic fatty liver disease (NAFLD) is limited. We sought to describe the long-term morbidity and mortality of patients with NAFLD with advanced fibrosis or cirrhosis by prospectively studying 247 such patients from four international centers (in Australia, USA, UK and Italy). Their natural history was then compared with 264 patients with HCV infection who were either naïve or non-responders to treatment. Both cohorts were Child-Pugh class A and had advanced fibrosis (stage 3) or cirrhosis (stage 4) confirmed by liver biopsy at enrollment. In the NAFLD cohort, followed up for a mean of 85.6 months (range, 6-297), there were 48 (19.4%) liver-related complications and 33 (13.4%) deaths or liver transplants. In the HCV cohort, followed up for 74.9 months (mean; range, 6-238), there were 47 (16.7%) liver-related complications and 25 (9.4%) deaths or liver transplants. When adjusting for baseline differences in age and gender, the cumulative incidence of liver-related complications was lower in the NAFLD than the HCV cohort ($P = 0.03$), including incident hepatocellular cancer (6 versus 18; $P = 0.03$), but that of cardiovascular events ($P = 0.17$) and overall mortality ($P = 0.6$) were similar in both groups. In the NAFLD cohort, platelet count, stage 4 fibrosis, lowered platelet count, and lowered serum cholesterol and alanine aminotransferase (ALT) levels were associated with liver-related complications; an aspartate aminotransferase/ALT ratio $>1$ and older age were associated with overall mortality, and higher serum bilirubin levels and stage 4 fibrosis were associated with liver-related mortality. Conclusions: Patients with NAFLD with advanced fibrosis or cirrhosis have lower rates of liver-related complications and hepatocellular cancer than corresponding patients with HCV infection, but similar overall mortality. Some clinical and laboratory features predict liver-related complications and other outcomes in patients with NAFLD. (HEPATOLOGY 2011;54:1208-1216)

See Editorial on Page 1118

Nonalcoholic fatty liver disease (NAFLD) has become the most prevalent cause of chronic liver disease worldwide.1-3 Regarded as the hepatic manifestation of the metabolic syndrome, NAFLD represents a histological spectrum of disease that extends from simple steatosis to steatohepatitis (NASH).1-5 NAFLD may be associated with advanced fibrosis or cirrhosis, which is a concern, as many of the liver-related complications and mortality (e.g., liver failure, varices, etc.) occur in these patients.6 In

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HCC, hepatocellular cancer; HCV, hepatitis C virus; HDL, high-density lipoprotein; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

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addition to an increasing need for transplantation,\textsuperscript{7} patients with NAFLD with and without cirrhosis may also develop hepatocellular cancer (HCC).\textsuperscript{8,9}

Despite its prevalence, the prognosis of NAFLD with advanced fibrosis or cirrhosis remains poorly studied. Previous studies have been hampered by problems with case ascertainment, definition, and have generally had limited numbers and/or follow-up, which could potentially lead to inaccurate estimates of disease burden.\textsuperscript{10-12} It is well established that cirrhotic patients presenting with overt synthetic liver dysfunction are more likely to develop liver-related complications and have a high overall mortality. However, some important aspects of the prognosis of patients with NAFLD still remain unclear. First, it is unclear how the long-term prognosis of patients with NAFLD compares with patients with liver disease of other etiologies, such as chronic hepatitis C virus (HCV) infection. Second, what are the risks of liver-related complications, including HCC, in patients with NAFLD with advanced fibrosis or cirrhosis and no overt synthetic dysfunction (i.e., Child-Pugh class A)? Third, the effect of NAFLD on non-liver-related sequelae, such as vascular outcomes (e.g., myocardial infarction, strokes, and vascular deaths), remains poorly described.\textsuperscript{13} Finally, it is unclear which, if any, risk factors can independently predict liver, vascular, and overall morbidity and mortality.

To answer these questions, we carried out an international, multicenter prospective study to assess the natural history and outcomes of liver biopsy-confirmed NAFLD with advanced fibrosis or cirrhosis from four medical centers. We sought to assess complications that occurred in these patients and identify the predictors of such events; we also compared their long-term morbidity and mortality to a group of patients with histologically confirmed chronic HCV infection and advanced fibrosis or cirrhosis.

**Patients and Methods**

**Participants and Setting.** A total of 247 Child-Pugh class A patients with biopsy-confirmed NAFLD and advanced fibrosis or cirrhosis comprised the NAFLD cohort. This cohort was recruited from 1984 to 2006. Patients were previously untreated and consecutively biopsied at four centers: Mayo Clinic (Rochester, MN) (n = 105); Newcastle Hospitals National Health Service Foundation Trust (Newcastle-upon-Tyne, UK) (n = 57); Westmead Hospital (Sydney, Australia) (n = 51); and University of Turin (Turin, Italy) (n = 34). The comparator cohort consisted of 264 patients diagnosed with HCV infection and advanced fibrosis or cirrhosis, who were also Child-Pugh class A, enrolled from 1987 to 2005. HCV infection was confirmed by a positive polymerase chain reaction at baseline in all patients. HCV subjects were seen and consecutively biopsied at Westmead Hospital (n = 209) and University of Turin (n = 55). They were either nonresponders to antiviral treatment (n = 224; 85%) or had never had any treatment for HCV infection (n = 40; 15%). These criteria were chosen because sustained virological response to anti-HCV therapy improves the outcomes of these patients. The study was approved by appropriate regulatory bodies at all centers, and written informed consent was obtained from all patients for participation in medical research.

NAFLD was diagnosed based on the following: (1) elevated aminotransferases for at least 6 months; (2) liver biopsy showing changes consistent with advanced fibrotic NAFLD (detailed below); and (3) exclusion of other etiologies, including viral, autoimmune, cholestatic, genetic, metabolic, alcoholic, or drug-induced liver diseases. These other etiologies were excluded using specific biochemical, clinical, radiological, and/or histological criteria. All patients had current and past consumption of ethanol less than 20 g per day on direct questioning of both the patients and a close relative.

A complete medical history and physical examination was undertaken. Body mass index (BMI) was calculated using the following formula: weight (in kilograms)/height$^2$ (in meters). Waist circumference (to the nearest half centimeter) was measured at the midpoint between the lower border of the ribcage and the iliac crest. Serum measurements included routine liver biochemistry (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels, total bilirubin, albumin, alkaline phosphatase, and gamma glutamyl transpeptidase),...
complete blood count, fasting glucose, fasting insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and total triglycerides, serology for hepatitis B and C viruses, iron studies, autoantibodies, alpha 1 antitrypsin levels and phenotype, and ceruloplasmin levels. Components of the metabolic syndrome, including central obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low HDL cholesterol, were recorded.

Liver Histology. Liver biopsies were stained with hematoxylin and eosin, Masson’s trichrome, and special stains for iron and copper. Liver biopsies were read by a single liver pathologist in each participating center. Histological features of NAFLD, such as steatosis, inflammation, hepatocyte ballooning, and fibrosis, were scored as previously described. Only those patients that had steatosis of at least 5% plus severe fibrosis (stage 3 [septal/bridging]) or cirrhosis (stage 4) fibrosis were included in this analysis. Other histological changes of steatohepatitis, such as inflammation and ballooning, were not required as inclusion criteria.

For HCV, the degree of fibrosis was scored according to the METAVIR scale as follows: stage 0, no fibrosis; stage 1, enlarged portal tract without septa; stage 2, enlarged portal tract with rare septa; stage 3, numerous septa without cirrhosis; stage 4, cirrhosis.

Data Collection. The start date for analyses was the date of liver biopsy, with any events occurring in the first 6 months excluded. Patients were monitored every 3-6 months and followed up until death or liver transplantation, whichever occurred first, or until data analysis. For those lost to follow-up, up-to-date clinical information was sought by the following: (1) contact with the primary care physician; (2) telephone interview; and (3) checking the respective death and transplant registries. Patients were censored at time of death or transplantation or last clinic visit, and those lost to follow-up were censored at the time last seen. All clinical outcomes were confirmed by a physician at each center, utilizing patient records and physician diagnoses.

The following outcomes were assessed: (1) liver complications, including liver failure, gastroesophageal varices (± hemorrhage), ascites, encephalopathy, hepatopulmonary syndrome, and HCC; (2) liver-related death or liver transplantation (for calculation of survival probability, transplantation was considered as an equivalent end-point); (3) all-cause mortality; and (4) total vascular events (including myocardial infarction, stroke, and vascular deaths). HCC was diagnosed if the following were present: (1) pathological changes consistent with HCC identified by histological examination of liver tissue obtained by fine-needle aspiration, liver biopsy, or liver explant at transplantation or autopsy or (2) one or more hepatic space-occupying lesions that had vascular patterns typical of HCC by angiography, triple-phase computed tomography, or magnetic resonance imaging.

All patients were followed according to standards of care and guidelines without experimental or therapeutic interventions for NAFLD or HCV. Weight management was performed with lifestyle intervention, such as dietary modification, and exercise was recommended at outpatients in overweight/obese patients. Other treatments, such as oral hypoglycemics, cholesterol-lowering medications, and antihypertensive medications, were only given in the context of management of concomitant diabetes mellitus, hypercholesterolemia, or hypertension, respectively. Neither pharmacological nor lifestyle interventions were recorded systematically after baseline.

Statistical Analysis. Statistical analyses were performed using SPSS version 13.0 (SPSS, Inc., Chicago IL). Results are reported as means ± standard deviation (SD) or frequency (i.e., percentage), as appropriate. Continuous variables were compared using the two-tailed Student’s t-test. Categorical data were compared using the chi-square test. Variables with a P value of ≤0.1 on univariate analysis were further analyzed by multiple logistic regression to determine the independent determinants of outcome variables. The cumulative probabilities of morbidity and mortality (including 95% confidence intervals [CIs]) were analyzed using the Kaplan-Meier method and using the date of the liver biopsy as time zero (baseline). The effect of individual variables upon morbidity and mortality were compared using log-rank tests. When assessing the effects of multiple variables on survival, Cox regression was used.

Results

Baseline Characteristics. Table 1 summarizes the baseline characteristics of the patient population. Among cases with NAFLD, mean age was 54.7 years, 60.5% were female, 91.5% were of white ethnicity, and mean BMI was 32.8 kg/m². More than half had concomitant metabolic morbidity, including 50% with diabetes, 44.1% with hypertension, and 12.1% with previous vascular disease. At baseline, metformin was used in one-third (34.4%) of patients, and statins in one-fifth (21.5%) of patients. Among cases with HCV, mean age was 48.3 years, 35.2% were female, 72.3% were white, and mean BMI was 27.3 kg/m². Average
The 264 HCV participants had a mean (± SD) follow-up of 74.9 (± 47.1) months (range, 6-238). Complete follow-up was achieved in 254 (96.2%) patients, and 10 (3.8%) patients were lost to follow-up. During follow-up, 47 (17.8%) patients developed liver-related complications. Nine (3.4%) developed gastroesophageal varices, 20 (7.6%) developed ascites, liver failure, and/or encephalopathy, and 18 (6.8%) patients developed HCC (10 of which were initially in stage 4 fibrosis). Nine (3.4%) had subsequent myocardial infarctions and 1 (0.3%) had a stroke (diagnosed as ischemic in etiology).

In the NAFLD cohort, the probability of liver-related, complication-free survival was 98.0%, 93.4%, and 81.5% at 12, 36, and 120 months, respectively, whereas in the HCV cohort, it was 98.4%, 93.5%, and 76.5% at 12, 36, and 120 months, respectively (Fig. 1A). In unadjusted comparison, there was a trend for more liver-related complications in the cohort with HCV infection than in the cohort with NAFLD (P = 0.09; Fig. 1A); there appeared to be stronger evidence of a difference between groups when adjusted in age, sex, BMI, and diabetes (P = 0.03; Fig. 1B,C). HCC occurred more commonly in HCV than in NAFLD (18 [6.8%] versus 6 [2.4%] respectively; P = 0.03), with time-to-event illustrated in Supporting Fig. 1. There was no significant difference in total vascular events between NAFLD and HCV groups (17 [6.9%] versus 10 [3.8%]; P = 0.17).

**Mortality (Liver-Related and All-Cause) and Liver Transplantation.** In the NAFLD cohort, there were a total of 33 deaths or liver transplants (13.4%). Of the 14 liver-related deaths and transplantations, 3 were related to HCC; there were 4 deaths related to other cancers and 1 definite vascular death. The probability of overall survival was 99.6%, 96.7%, and 81.6% at 12, 36, and 120 months, respectively (Fig. 2A). In the HCV cohort, there were a total of 25 deaths or liver transplants (9.5%). Of the 21 liver-related deaths and transplantations, 12 were related to HCC; there was 1 definite vascular death and 3 deaths from unknown causes. The probability of overall free survival was 99.2%, 98.3%, and 82.0% at 12, 36, and 120 months, respectively (Fig. 2A). Overall mortality was similar in both cohorts (P = 0.38; Fig. 2A), with no evidence of differences after adjustment by differences between groups in age, sex, BMI, diabetes, and dyslipidaemia (P = 0.6; Fig. 2B,C).

**Liver-Related Complications and Overall Mortality by Fibrosis Stage.** In the NAFLD group, there was strong evidence of differences between fibrosis stage 3 and 4 for total liver-related complications (P < 0.001)
and some evidence for overall mortality ($P = 0.05$), as illustrated in Supporting Fig. 2A,B. In the HCV group, there was little evidence of differences between fibrosis stage 3 and 4 for total liver-related complications ($P = 0.18$) and some evidence for overall mortality ($P = 0.04$), as illustrated in Supporting Fig. 3A,B.

**Independent Predictors for Liver-Related Complications in the NAFLD Cohort.** Univariate models to characterize differences in the NAFLD group are shown in Supporting Table 1, and a summary of the multivariate predictive factors for all categories of outcome are shown in Table 2. Stage 4 fibrosis, past history of coronary heart disease, lower serum levels of cholesterol, lower levels of ALT, and lower platelet count were all independently associated with total liver-related complications. Independent predictors were also identified for the development of ascites (e.g., lower platelet count), encephalopathy (e.g., older age), gastroesophageal varices (e.g., stage 4 fibrosis, lower levels of ALT, lower platelet count, and lower levels of cholesterol), and myocardial infarction (e.g., past medical history of hypercholesterolemia and lower HDL cholesterol). No factors were identified as predictors for HCC or stroke. All these differences remained unaffected when the center variable was included in the models.

**Independent Predictors for Mortality in the NAFLD Cohort.** Univariate models to characterize differences in the NAFLD cohort are shown in Supporting Table 2, and a summary of the multivariate predictive factors are shown in Table 2. By multivariate analysis and adjusting for center, older age and higher AST/ALT ratio were independently associated with overall mortality. Stage 4 fibrosis and higher serum bilirubin levels were independently associated with liver-related mortality. History of diabetes mellitus and hypercholesterolemia were associated with vascular events (i.e., nonfatal myocardial infarction, nonfatal stroke, and vascular death) and vascular-related death.

**Discussion**

In this large, multicenter study from four countries, we report the natural history of the largest cohort of biopsy-proven NAFLD with advanced fibrosis or cirrhosis to date. The NAFLD patients had well-compensated liver disease and no overt hepatic synthetic dysfunction at presentation, and they were compared with patients with HCV infection with advanced fibrosis or cirrhosis of the same functional status. There are important long-term differences, notably less liver-related complications and less HCC risk in patients with NAFLD, as compared to patients with HCV infection, but also remarkable long-term similarities for vascular disease and overall mortality. In addition, we were able...
to identify independent risk factors for liver- and vascular-related complications and mortality in NAFLD.

This study has a number of strengths, including its relatively large sample size and the recruiting of incident cases who were extensively assessed and biopsied to ascertain the diagnosis. In particular, biopsy confirmation avoids many of the pitfalls of studies that have described cryptogenic cirrhosis associated with risk factors for NAFLD without formal histological classification. Patients were seen in three different continents, and, hence, the results should be generalizable to at least these populations, although evidence in non-Caucasian patients is lacking. Approximately 95% of the total cohort had complete follow-up, allowing an accurate quantification of outcomes. All the centers specialize in the management of NAFLD and HCV, meaning that patients were treated according to guidelines, were regularly followed up, and causes of events, especially those related to the liver, were verified.

Prospective observational studies do have inherent limitations and biases, including those of referral (i.e., all being specialist hepatology centers), lead time (i.e., timing of diagnosis-altering outcomes), and selection (e.g., HCV nonresponders being more likely to progress). Because histology was interpreted by independent pathologists at each center, there could be some inter-rater variability—however, this was likely to be low, as experienced liver pathologists reviewed samples, and fibrosis stages 3 and 4 have the best kappa scores, as compared to other histological features. In particular, biopsy confirmation avoids many of the pitfalls of studies that have described cryptogenic cirrhosis associated with risk factors for NAFLD without formal histological classification. Our histological criteria were strict to ensure that burned-out autoimmune hepatitis was not mistaken as a NAFLD case, for example. We cannot rule out NASH cases being excluded (e.g., those with NASH and steatosis <5%), but, as a result of the workup to exclude other etiologies, all included cases were managed clinically as NAFLD. Logistically, it was not possible to match every patient with NAFLD by age and gender with patients with HCV infection; however, only age was shown to have an independent effect on outcomes. We also adjusted the comparisons by age, sex, BMI, and the presence of diabetes and dyslipidaemia without discernible differences.

There may be residual confounding by some parameters: For example, diabetes status differed significantly between NAFLD and HCV, and even though this was adjusted for, this cannot account for severity of dysglycemia. Moreover, follow-up for medical problems that may have an effect, such as de novo diabetes mellitus, were not assessed systematically (although insulin resistance may play a role in HCV as well as in NAFLD). Nor can we rule out effects of later medications for the treatment of comorbidities, although no pharmacological treatments have been shown
reliably to have a substantive effect on liver fibrosis in NAFLD.18 This also applies to any effects of nonpharmacological treatments, such as exercise or diet.19 Practice and follow-up obviously varied between the centers, although this does not affect the systematic prospective methodology used, nor should it significantly affect the event predictors.

Compared to the general population, NAFLD has been associated with an increased risk of overall death (standardized mortality ratio: 1.34; 95% CIs: 1.003-1.76) in a community-based study of 420 patients from the United States.20 In a similar Swedish study, just over 5% of the 129 NAFLD patients enrolled went on to develop end-stage liver disease.21 In both studies, there was a higher vascular- and liver-related mortality in patients with NAFLD (as compared to the general population of the same age and sex).

In contrast to patients with other liver diseases, the short-term prognosis of NAFLD is largely excellent, but longer term prognosis depends crucially on histological stage at presentation.6,22 In patients with bland steatosis, two studies have reported either nil23 or minimal progression24 to advanced disease over a median of 11.5 and 16.7 years, respectively. For those with NASH on baseline liver biopsy, 11% went on to develop cirrhosis and ~40% of patients die from any cause within 15 years (of which 7.3% are from liver-related complications, especially in those with advanced fibrosis or cirrhosis).6 Studies with subsequent liver biopsy have also prospectively evaluated the risk of fibrosis progression over time. One hundred three patients underwent two liver biopsies 1-21 years apart: Baseline low fibrosis stage, diabetes, and greater BMI were independently associated with fibrosis progression.25 In a similar study from Sweden, 70 patients underwent two liver biopsies 10-16 years apart; progression of fibrosis stage occurred in 41% and was associated with diabetes, weight gain, and increased insulin resistance.21

A case-control study of 23 patients from Sydney with cirrhotic stage NASH, compared to those with HCV, showed no difference between liver-related deaths or all-cause mortality between groups after adjustment for baseline differences, despite a trend toward improved survival in NASH.12 A larger case comparison from Virginia compared 152 patients with cirrhosis resulting from NASH with 150 subjects with HCV nonresponders.26 The 10-year survival in the NASH group was 80.9%, significantly better than in the HCV controls of similar age, sex, and Child-Pugh score, principally the result of a lower risk of hepatic decompensation in the NASH cohort. However, the Virginia study examined less Child-Pugh class A patients (n = 74) than in our study (n = 247). More recently, a Cleveland Clinic prospective study found lower rates of HCC in 195 NASH, compared to 315 HCV, cirrhotics (annual risk 2.6% versus 4%; P = 0.09), although their NASH group also contained those with cryptogenic cirrhosis and former heavy drinkers.27

### Table 2. Multivariate Analyses for Overall Mortality, Liver-Related Mortality, Overall Vascular Events, Myocardial Infarction, Total Liver Events, Varices, Ascites, and Encephalopathy in the NAFLD Cohort*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td></td>
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<tr>
<td>AST/ALT &gt; 1</td>
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<td>(1.10-12.68)</td>
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<td>Age (increase in 10 years)</td>
<td>1.55</td>
<td>(1.02-2.35)</td>
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<td>Liver-related mortality</td>
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<td>Bilirubin (increase in 10 μmol/L)</td>
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<td>(1.09-4.22)</td>
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<tr>
<td>Fibrosis stage</td>
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<td>Vascular event and death (APT)</td>
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<tr>
<td>Diabetes</td>
<td>10.43</td>
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<td>Hypercholesterolaemia</td>
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<td>Myocardial infarction</td>
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<td>HDL (decrease in 0.1 mmol/L)</td>
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<td>(1.73-50.71)</td>
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<td>CAD</td>
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<td>(1.04-8.58)</td>
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<td>Platelets (decrease in 20 × 10^5/L)</td>
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<td>Ascites</td>
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<tr>
<td>Encephalopathy</td>
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<tr>
<td>Age (increase in 10 years)</td>
<td>3.42</td>
<td>(1.09-10.58)</td>
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<td>(1.02-1.38)</td>
<td>0.04</td>
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</table>

*n = 247.

Abbreviations: NAFLD, non alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APT, Antiplatelet Trialists’ composite outcome: first nonfatal myocardial infarction, nonfatal stroke or any vascular death; HDL, high-density lipoprotein; CAD, coronary artery disease.
This study adds important new information to our knowledge on the natural history of patients with well-compensated NAFLD (Child-Pugh class A at enrollment): A lower stage of liver fibrosis (stage 3 versus stage 4 cirrhosis) is associated with an increased risk of liver complications and, potentially, overall mortality. NAFLD appears to have lower rates of liver-related complications, but similar overall mortality, as compared to HCV patients, even when adjusting for age (and other potential confounders). One of the key and controversial complications was the risk of HCC in NAFLD. In this large cohort, HCC was significantly more common in HCV than NAFLD (6.8% versus 2.4%, respectively). The HCV cohort had an approximate 0.15% risk per annum of HCC development versus 0.05% risk per annum in NAFLD. The figures found in our study are much lower than those reported in the NASH studies from Virginia (17% versus 6.7%) and the Cleveland Clinic (20.3% versus 12.8%).26,27 “This may be the result of differences in risk factors for HCC among the patient populations (e.g., alcohol consumption and comorbidities), the inclusion of more advanced liver disease (e.g., Child-Pugh class B and C,26 higher MELD score,27 and NASH histology in both) or reduced random error with our larger sample sizes. Cirrhosis per se increases the risk of HCC,28 but there is wide variation in carcinogenic risk, depending on disease etiology: Large case-control studies indicate that diabetes increases the risk of HCC by 1.3- to 2.4-fold, whereas viral hepatitis increases this risk 13- to 19-fold.29 Taken together, we interpret the present data as indicating that the incidence of HCC is lower in NAFLD than in chronic HCV infection. However, given the high prevalence of NAFLD in the community, the population-attributable risk of HCC related to NAFLD is still considerable (~13%-20%).12

As hypercholesterolemia and diabetes are strongly associated with major vascular events, a holistic approach to NAFLD treatment is needed, including adequate treatment of metabolic conditions (e.g., diabetes and dyslipidemia).18,19 As well as the emerging relevance of NAFLD for cardiovascular diseases,30 this collaborative study highlights the risk of liver-related events and mortality in NAFLD with advanced fibrosis. The risk factors we identified for liver-related complications are of relevance to the practicing clinician, including progressive rises in serum bilirubin and fibrosis stage for liver-related mortality and a low platelet count for both ascites and varices (consistent with a portal hypertensive etiology).

The MELD score did not predict outcomes in our NAFLD cohort, which can be explained by patients being Child-Pugh class A at enrollment rather than assessment for liver transplantation. Many of the factors that play a role in the MELD equation, such as age, were independent predictors (in this case, of overall mortality and encephalopathy). Interestingly, the AST/ALT ratio (commonly used to differentiate fatty liver clinically from other etiologies) also served as a predictor of overall mortality, having previously been shown to independently distinguish between patients with and without advanced liver fibrosis.51

In summary, in this multicenter, collaborative study, there were independent risk factors for vascular, liver, and all-cause outcomes in patients with NAFLD with advanced fibrosis or cirrhosis who had no overt evidence of hepatic decompensation at enrollment. At these histological stages, NAFLD appears to lead to lower rates of liver-related complications and lower rates of HCC than patients with HCV infection of a similar disease stage, albeit the overall mortality in both conditions seems to be similar. However, larger, prospective studies are necessary to shed further insights on the impact of NAFLD on liver- and vascular-related morbidity and mortality.

References


