Long-Term Outcomes of Cirrhosis in Nonalcoholic Steatohepatitis Compared With Hepatitis C

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Data on the long-term outcome of nonalcoholic steatohepatitis (NASH)-associated cirrhosis are few, and most reports describe cases of cryptogenic cirrhosis associated with risk factors for NASH but without histologic definition. In this prospective cohort study, we describe the long-term morbidity and mortality of 23 patients with NASH-associated cirrhosis defined by strict clinicopathologic criteria. Outcomes were compared with 46 age- and gender-matched patients with cirrhosis from chronic hepatitis C virus (HCV) infection: 23 untreated and 23 nonresponders to antiviral therapy. During follow-up (mean, 84 months; median, 60 months; range, 5-177 months), 9 of the 23 NASH-associated cirrhosis cases developed liver-related morbidity (8 ascites and/or encephalopathy, 1 variceal bleeding). The probability of complication-free survival was 83%, 77%, and 48% at 1, 3, and 10 years, respectively, and the cumulative probability of overall survival was 95%, 90%, and 84% at 1, 3, and 10 years, respectively. Five deaths were from liver failure, 1 from a non-liver-related cause. By multivariate analysis, bilirubin (P = .02) and platelet (P = .04) were independent predictors of complication-free survival; bilirubin (P = .05) was the only predictor for overall survival. After controlling for these factors, there was no difference in complication-free or overall survival between the NASH-cirrhosis cohort and either group of HCV-cirrhosis. However, 8 cases of liver cancer occurred in the HCV-cirrhosis groups compared with none among NASH cases. In conclusion, liver failure is the main cause of morbidity and mortality in NASH-associated cirrhosis. The prognosis is either similar or less severe than HCV-cirrhosis, except that HCC appears less common. (HEPATOLOGY 2003;38:420-427.)

Liver-related morbidity and mortality in nonalcoholic steatohepatitis (NASH) occurs principally among those with cirrhosis, a finding similar to the natural history of hepatitis C. There is, however, a paucity of data on the natural history of cirrhosis attributable solely to host metabolic factors (NASH). In large part, this relates to the lack of accepted histologic and clinical criteria for the diagnosis of “NASH-associated cirrhosis” as opposed to “cryptogenic cirrhosis” occurring in people with risk factors for NASH. These definitional problems are compounded by reports that the features of steatohepatitis on liver biopsy may disappear with fibrotic progression.1 Although disease progression in NASH is slow,1 it is unclear whether clinical progression and liver complications are inevitable or whether the rate of progression is faster or slower than that in other liver diseases, such as hepatitis C. Prospective outcome studies of NASH are difficult to perform because of the need for extended follow-up, the possibility of death from other causes (especially cardiovascular disease and cancer),2 and the reluctance to undertake serial liver biopsy because of the perceived benign natural history and lack of specific therapies.

In chronic hepatitis B and C, liver cancer has become a major cause of mortality. A recent report also suggests an alarmingly high incidence of hepatocellular carcinoma (HCC; 30%) in overweight patients with cryptogenic cirrhosis.3 However, although cases of HCC complicating NASH are well documented,4,5 clinical impressions are...
that metabolic liver disease is a rare cause of HCC. We therefore undertook the present study to document the long-term morbidity and mortality among a prospectively followed cohort with NASH-associated cirrhosis that we defined using strict clinicopathologic criteria. We compared the rates of liver failure and HCC to an age- and gender-matched cohort of patients with chronic hepatitis C. To allow for possible differences in the selection of hepatitis C virus (HCV)-infected cases, particularly duration and functional severity of cirrhosis, we studied separate groups of untreated HCV-infected subjects and those with nonresponse to previous antiviral therapy and adjusted for any difference in disease severity using a multivariate model.

**Patients and Methods**

**Patient Population.** We identified 23 consecutive patients with cirrhosis from a database of 103 persons with NASH at Westmead Hospital. About two thirds of these individuals have been the subject of previous reports.6-7 Only those with histologic features of NASH and cirrhosis, together with known clinical risk factors, were included. The risk factors included overweight (body mass index [BMI], 25 to 29.9 kg/m2), obesity (BMI ≥ 30), type 2 diabetes mellitus, or hyperlipidemia. In all except 1 patient, the presence of at least 1 of these clinical risk factors had been documented for more than 5 years preceding the diagnosis of cirrhosis. The remaining patient presented with polyuria and polydipsia and a fasting plasma glucose of 18.9 mmol/L 2 months before the diagnosis of cirrhosis was made and was presumed to have had undiagnosed diabetes mellitus for some years prior to this.

We devised a working classification for patients with micronodular cirrhosis and clinical risk factors for NASH and categorized cases into 4 histologic groups: (1) definite NASH-associated cirrhosis, (2) probable NASH-associated cirrhosis, (3) possible NASH-associated cirrhosis, and (4) cryptogenic cirrhosis with clinical risk factors for NASH (see Discussion section regarding the rationale for this classification). Details of assignment into these operational groups are presented in Table 1, but it is important to note that all cases studied here were either “definite” or “probable” cases of NASH cirrhosis. All biopsy specimens were stained with hematoxylin and eosin, reticulin, and Gomori trichrome stains and were reported by an experienced hepatopathologist (J.G.K.) according to the scoring system of Brunt et al.8

Other disorders causing steatohepatitis or liver disease were excluded, as previously reported.7 To diminish any contribution to survival characteristics from lead-time bias, we excluded patients with a hepatic mass at presentation. Details regarding alcohol consumption were obtained independently by at least 2 physicians and confirmed by close family members. All patients had current and past daily alcohol intake of less than 40 g per week. We selected this level of consumption (as opposed to 140 g per week9,10) to exclude an interactive role of ethanol consumption in this study of patients with cirrhosis attributed exclusively to metabolic determinants. The study protocol was approved by the Human Ethics Committees of the Western Sydney Area Health Service.

**Data Collection.** Age, gender, height, and weight were documented at the time cirrhosis was detected; in all except 2 cases, this was taken as the time of liver biopsy. In the other 2 cases, the time of cirrhosis detection was taken as the time of development of ascites, and, to avoid confounding calculations of BMI, their weight was taken as that prior to the onset of ascites. A history of type 2 diabetes mellitus, hypertriglyceridemia, arterial hypertension, or cardiovascular or cerebrovascular disease was ascertained at the time of detecting cirrhosis, and subsequent development of these features was noted during follow-up and confirmed with the caring physician. Laboratory data recorded at the time of liver biopsy included the following: serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum bilirubin, serum albumin, prothrombin time, and platelet count.

**Comparison Group: Patients With HCV-Cirrhosis.** The outcome of NASH-associated cirrhosis was compared with patients with chronic HCV-associated cirrhosis. Two groups of age- (within 5 years) and gender-matched HCV-infected patients were identified from a database of 455 patients reported earlier11 and followed prospectively. All patients were selected in a blinded fashion on the basis of age, gender, and antiviral treatment status, without knowledge of clinical outcomes. The first

**Table 1. Proposed Pathologic Criteria for the Diagnosis of NASH-Associated Cirrhosis**

<table>
<thead>
<tr>
<th>Category</th>
<th>No.*</th>
<th>Steatosis</th>
<th>Inflammatory Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Definite†</td>
<td>20</td>
<td>Yes</td>
<td>Intralobular mixed inflammatory foci, including neutrophils and mononuclear cells</td>
</tr>
<tr>
<td>2. Probable</td>
<td>3</td>
<td>Yes</td>
<td>Intralobular mononuclear inflammation</td>
</tr>
<tr>
<td>3a. Possible</td>
<td>None</td>
<td>No</td>
<td>Intralobular mixed inflammation</td>
</tr>
<tr>
<td>3b. Possible</td>
<td>None</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>4. Cryptogenic cirrhosis‡</td>
<td>None</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

*Number of cases in this study.
†Patients with a current liver biopsy specimen consistent only with cryptogenic cirrhosis (category 4) but an earlier biopsy specimen demonstrating steatohepatitis would be considered as “Definite NASH-associated cirrhosis.”
‡Patients with risk factors for NASH and careful exclusion of all other known causes of liver disease (see Materials and Methods section).
group consisted of 23 patients with no past antiviral treatment ("untreated group"). Given the inherent potential for selection bias toward more severe liver disease in this cohort (compared with the patients with NASH), we identified a second subset of 23 HCV-infected patients who had received antiviral treatment (interferon alfa monotherapy [19 cases] or combination therapy with interferon alfa and ribavirin [4 cases]) but were nonresponders ("nonresponder group"). In 4 cases, age-matched HCV patients (3 in the untreated group and 1 in the nonresponder group) could not be obtained, and HCV patients with an age difference of 7 or 8 years (2 were older and 2 were younger) were used.

All HCV patients had detectable HCV RNA by reverse-transcriptase polymerase chain reaction (Amplicor HCV; Roche Diagnostics, Branchburg, NJ). Cirrhosis was confirmed histologically in all but 3 of the HCV infected individuals. In the other 3 patients, 2 had unequivocal evidence of cirrhosis (portal hypertention with splenomegaly and thrombocytopenia). In addition, we chose one patient with evidence of ascites as an appropriate match to one of the NASH subjects with ascites. No HCV patient had alcohol intake greater than 40 g/wk within 6 months of their liver biopsy: 4 patients had a past alcohol intake of 10 to 40 g/d, and 5 patients had an intake of more than 40 g/d prior to the diagnosis of cirrhosis. These 9 cases were excluded for comparisons of perisinusoidal/pericellular fibrosis and ballooning degeneration with that in NASH-associated cirrhosis. Liver biopsy specimens were available for review in 26 of the 37 patients with HCV-cirrhosis.

Assessment of Outcomes. Patients were monitored clinically every 6 months until data analysis. For those lost to follow-up, up-to-date clinical information was sought by the following: (1) mailing a written questionnaire, (2) telephone interview, (3) contact with the primary care physician, and (4) checking the state (New South Wales) Registry of Births, Deaths, and Marriages; the NSW Cancer Registry; and the Australian National Liver Transplant Database at Royal Prince Alfred Hospital. Clinical events reported by the patients were confirmed by contact with the caring physician. Cases that remained lost to follow-up were censored at the time last seen.

The following outcomes were assessed: (1) liver-related morbidity (ascites, hepatic encephalopathy, variceal bleeding, HCC); (2) liver-related death or liver transplantation (for calculation of survival probability, liver transplantation was considered as an equivalent end point); and (3) other causes of death, which were determined from the hospital medical file, death certificate, and/or the above registries. HCC was diagnosed if the following were present: (1) pathologic changes consistent with HCC were identified by cytologic or histologic examination of liver tissue obtained by fine-needle aspiration, liver biopsy, or liver explant at transplantation or at autopsy; or (2) 1 or more hepatic space-occupying lesions were present at ultrasonography, or computed tomography that were shown to have vascular patterns typical of HCC by angiography, triple-phase spiral computed tomography, or magnetic resonance imaging.

Statistical Methods. Means and standard deviations were used as summary statistics for data that appeared to be normally distributed, whereas medians and quartiles were adopted to express skewed data and the proportion in each class for categorical data. Analysis of variance was used to test for homogeneity of the distributions of continuous variables across the 3 patient groups. \( \chi^2 \) Tests were used for categorical variables.

To examine differences between the patient groups, we performed 3 separate survival analyses, from cirrhosis detection to the following: (1) first liver-related morbidity ("complication-free survival"), (2) liver-related death or liver transplantation ("liver-related mortality"), and (3) death from any cause or liver transplantation ("all-cause mortality"). The cumulative probabilities to morbidity and mortality (including 95% confidence intervals [CI]) were analyzed using Kaplan-Meier’s methods. Both univariate and multivariate stratified Cox regression analyses of the survival times were used to identify variables associated with an increased risk of poor outcomes. Allowance was made in the analysis for the matched nature of the study design by considering each matched set as a stratum. The statistical software package SPSS for Windows (SPSS Inc., version 10.0, Chicago, IL) was used to analyze the data, and \( P \leq .05 \) was considered a significant difference.

Results

Characteristics of Patients With NASH-Associated Cirrhosis Compared With HCV Cirrhosis. Among NASH cases, 70% were female patients, and the mean age was 52.6 ± 13.6 (range, 25-74) years (Table 2). Four patients were ≤36 years of age at the time cirrhosis was diagnosed. Except for 1 case, all were overweight (6/23, 26%) or obese (16/23, 70%), mean BMI was 32.0 ± 5.1. Fifteen patients (65%) had diabetes mellitus, 7 (30%) had hyperlipidemia, and almost half (11/23, 48%) had hypertension. Diabetes mellitus was more common among NASH than HCV-cirrhosis (\( P < .04 \)) (Table 3). Four patients developed vascular events (2 coronary artery disease, 1 cerebrovascular disease, 1 with both complications), but vascular events also supervened in 4 patients with HCV-cirrhosis, 2 in each group.
Patients with NASH-associated cirrhosis had lower serum ALT levels compared with both “untreated” and “nonresponder” HCV groups (P < .001) (Table 3). By other criteria, the “untreated” HCV-cirrhosis group had more severe liver disease compared with NASH-cirrhosis and the “nonresponder” HCV-cirrhosis groups, including lower serum albumin (P = .01) and platelet count (P < .001).

Liver Histology. Twenty of 23 subjects (87%) had definite NASH-associated cirrhosis (see Table 1). In the remaining three subjects with probable NASH-associated cirrhosis, steatosis, and mononuclear inflammation were evident. Most cases (61%) had grade 1 necroinflammatory activity, and 35% had grade 2 activity. Perisinusoidal/pericellular fibrosis was present in 18 (78%) cases and ballooning degeneration of hepatocytes in 21 (91%) (Table 2). Among the 26 HCV patients with liver biopsy specimens available for review (in whom current and past alcohol intake was <10 g/d), perisinusoidal/pericellular fibrosis was present in 8 (31%) cases, and ballooning degeneration was seen in 10 (38%) cases.

Natural History of NASH-Associated Cirrhosis Compared With HCV-Cirrhosis, Complication-Free Survival. During a mean follow-up of 84 months (median, 60 months; range, 5-177 months), 9 (38%) patients with NASH-cirrhosis developed liver-related morbidity. Eight patients developed ascites and/or encephalopathy, and 1 patient experienced bleeding esophageal varices (endoscopically proven). None developed HCC. The probability of “complication-free survival” after the diagnosis of cirrhosis was 83% (CI: 67%-98%), 77% (CI: 59%-95%), and 48% (CI: 20%-77%) at 1, 3, and 10 years, respectively (Fig. 1).

The “untreated HCV-cirrhosis” group was followed-up for a mean of 80 months (median, 81 months; range, 4-170 months), during which 13 patients (55%) developed liver-related morbidity (5 cases ascites and/or encephalopathy, 5 cases HCC, and 3 cases variceal bleeding). The probability of “complication-free survival” after the diagnosis of HCV-cirrhosis was 83% (CI: 67%-98%), 78% (CI: 60%-95%), and 34% (CI: 11%-58%) at 1, 3, and 10 years, respectively (Fig. 1). In the “nonresponder” HCV group with a mean follow-up of 83 months (median, 83 months; range, 11-176 months), 9 patients (38%) experienced liver-related morbidity. There were 6 cases of ascites and/or encephalopathy and 3 cases of HCC. The probability of “complication-free survival” after the diagnosis of cirrhosis was 96% (CI: 87%-100%), 91% (CI: 80%-100%), and 56% (CI: 28%-84%) at 1, 3, and 10 years, respectively (Fig. 1).

Using multivariate analysis with Cox’s model, serum bilirubin and platelet count were independent predictors of “complication-free survival.” Thus, each 5 μmol/L increase in bilirubin was associated with a 2.2-fold (hazard ratio [HR]) increase in risk of liver-related morbidity (P =

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NASH n = 23</th>
<th>Untreated HCV n = 23</th>
<th>Nonresponder HCV n = 23</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr), mean ± SD</td>
<td>52.6 ± 13.6</td>
<td>52.6 ± 11.4</td>
<td>51.4 ± 12.8</td>
<td>.93</td>
</tr>
<tr>
<td>ALT (U/L), mean ± SD</td>
<td>58 ± 32</td>
<td>132 ± 93</td>
<td>196 ± 113</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Albumin (g/L), mean ± SD</td>
<td>41.7 ± 5.1</td>
<td>37.4 ± 5.3</td>
<td>41.0 ± 4.6</td>
<td>.012</td>
</tr>
<tr>
<td>Bilirubin (μmol/L), mean ± SD</td>
<td>18.0 ± 12.9</td>
<td>20.7 ± 20.9</td>
<td>15.8 ± 8.8</td>
<td>.6</td>
</tr>
<tr>
<td>Platelet (×10^9/L), mean ± SD</td>
<td>194 ± 87</td>
<td>100 ± 45</td>
<td>119 ± 54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prothrombin time (s), mean ± SD</td>
<td>13.7 ± 1.3</td>
<td>14.7 ± 1.7</td>
<td>14.1 ± 1.5</td>
<td>.07</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>.04</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>.9</td>
</tr>
<tr>
<td>Cerebral vascular disease</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>.8</td>
</tr>
</tbody>
</table>
.02, 95% CI: 1.1-4.5), whereas each $10 \times 10^9$/L decrease in platelet count was associated with a 1.2-fold increase in risk ($P = .04, 95\% \text{ CI}: 1.0-1.5$). After controlling for these factors, there was no difference in “complication-free survival” between the NASH-associated cirrhosis cohort and “untreated” or “nonresponder” HCV patients with cirrhosis ($P = .9$ and $P = .4$ respectively). It is noted that separate analyses with exclusion of the 4 HCV cases who were imperfectly matched for age or the 1 case who presented with ascites (see Materials and Methods section) did not alter this result.

“Liver-Related” and “All-Cause” Mortality. Five patients with NASH-associated cirrhosis died from liver failure and 1 from metastatic melanoma. None died from cardiovascular events. The cumulative probability of survival related to “all-cause mortality” was 95% (CI: 86%-100%), 90% (CI: 77%-100%), and 84% (CI: 66%-100%) at 1, 3, and 10 years, respectively (Fig. 2). The exclusion of non-liver-related death (“liver-related mortality”) did not alter these survival probabilities (Fig. 3).

In the “untreated HCV-cirrhosis” group, 7 died from a liver-related death or underwent hepatic transplantation (4 cases of liver failure, 2 of HCC, 1 liver transplantation). One patient died from acute myocardial infarction. The probability of survival related to liver-related mortality), the probability of survival was 96% (CI: 87%-100%), 91% (CI: 79%-100%), and 55% (CI: 24%-87%) at 1, 3, and 10 years, respectively (Fig. 3).

In the “nonresponder HCV-cirrhosis” group, 7 patients died from a liver-related death or underwent hepatic transplantation (4 cases of liver failure, 2 of HCC, 1 liver transplantation). One patient died from acute myocardial infarction. The probability of survival related to

### Figures

**Fig. 1.** Cumulative probability of complication-free survival for NASH-associated cirrhosis (thick line), matched untreated HCV-cirrhosis (thin line), and matched nonresponder HCV-cirrhosis (dotted line). There was no difference in complication-free survival between the 3 groups after adjustment for the difference in baseline variables (Cox model, see text).

**Fig. 2.** Cumulative probability of overall survival for NASH-associated cirrhosis (thick line), matched untreated HCV-cirrhosis (thin line), and matched nonresponder HCV-cirrhosis (dotted line). There was no difference in overall survival between the 3 groups after adjustment for the difference in baseline variables (Cox model, see text).

**Fig. 3.** Cumulative probability of survival (censoring nonliver-related deaths) for NASH-associated cirrhosis (thick line), matched untreated HCV-cirrhosis (thin line), and matched nonresponder HCV-cirrhosis (dotted line). There was no difference in survival (censoring nonliver-related deaths) after adjustment for the difference in baseline variables (Cox model, see text).
“all-cause mortality” was 100%, 100%, and 59% (CI: 32%-87%) at 1, 3, and 10 years, respectively (Fig. 2). After exclusion of non-liver-related deaths (“liver-related mortality”), the probability of survival was 100%, 100%, and 66% (CI: 38%-94%) at 1, 3, and 10 years, respectively (Fig. 3).

By multivariate analysis, serum bilirubin was the only independent predictor for “liver-related mortality” ($P = .05$, HR = $1.6$ [CI: 1.0-2.6] for each 5 $\mu$mol/L increase in bilirubin) and for “all-cause mortality” ($P = .05$, HR = $1.6$ [CI: 1.0-2.4] for each 5 $\mu$mol/L increase in bilirubin). After controlling for the effect of bilirubin, there was no difference between the NASH patients and the “untreated” or “nonresponder” HCV groups in the rate of liver-related death or liver transplantation ($P = .6$ and $P = .2$, respectively) or in the rate of all-cause death or liver transplantation ($P = 1.0$ and $P = .4$, respectively). The exclusion of the 4 HCV-infected patients who were not matched for age or the 1 patient who presented with ascites (see Materials and Methods section) did not alter these results.

**Discussion**

In this prospective study, we used an operational definition for the histologic classification of cirrhosis associated with NASH and found that the prognosis for patients with a “definite” or “probable” diagnosis of NASH-associated cirrhosis was similar to or better than that of HCV-associated cirrhosis. Furthermore, liver failure was the cause of death in the majority of cases of NASH-associated cirrhosis, even though most had risk factors for cardiovascular disease. However, although HCC was confirmed as a common complication ($\sim 2.5\%$ per annum) of hepatitis C cirrhosis, no case of HCC was observed among 23 patients with cirrhosis caused by NASH during 7 years (mean) follow-up.

Previous studies have examined patients with cryptogenic cirrhosis and clinical risk factors for NASH. It now seems likely that a proportion of cases of “cryptogenic cirrhosis” represent “burnt-out” NASH. However, other potential causes include previous (or occult) alcohol abuse, “burnt-out” (inactive) autoimmune hepatitis, occult viral infection (especially hepatitis B), and heterozygous $\alpha$-1 antitrypsin deficiency. In the present cohort, case definition required histologic features consistent with NASH, in addition to clinical risk factors for more than 5 years (obesity, diabetes, and hyperlipidemia). We also required exclusion of all but minimal levels of current and past alcohol consumption ($<40$ g/wk). To better distinguish NASH-associated cirrhosis from known and possibly other yet to be defined diseases, we proposed 4 histopathologic categories (Table 1). Only steatosis and inflammation were included in the diagnostic criteria because interpretation of the other hallmarks of NASH such as acinar zone 2 or 3 perisinusoidal/pericellular fibrosis and ballooning degeneration is difficult in the setting of cirrhosis. Thus, established micronodular cirrhosis considerably distorts the hepatic architecture, with portal-central bridging fibrosis and incorporation of terminal hepatic venules (central veins) into the fibrous septa where they may be difficult to identify. Assessment of zonality of pericellular fibrosis is thus unreliable in advanced cirrhosis. Furthermore, ballooning degeneration of hepatocytes has a similar appearance to swelling of hepatocytes or “feathery degeneration” found with chronic cholestasis that can be the result of architectural distortion in cirrhosis. Our own data underscore this lack of specificity of perisinusoidal/pericellular fibrosis and ballooning degeneration for NASH biopsy specimens with cirrhosis; thus, these features were present in 31% and 38% of HCV cases, respectively.

The majority of NASH cirrhosis patients in this study were female (70%), similar to other series that identified a predominance of females among NASH patients with advanced fibrosis or cirrhosis. This female patient preponderance is a major distinction between the present study and reports of the outcome of cryptogenic cirrhosis without histologic definition of NASH. With the exception of 1 patient, all subjects in our NASH cohort had at least 1 predictor of fibrosis as identified by Angulo et al., namely, age $\geq$45 years, obesity, diabetes mellitus, and AST/ALT $>1$. Most (18/23, 78%) patients had more than 1 predictor. However, it is noteworthy that the youngest patient in this cohort of NASH cirrhosis was 25 years of age, and 4 were 36 years of age or younger at the time of cirrhosis detection. The recent reports of NASH-associated severe fibrosis and cirrhosis in the pediatric population together with the development of cirrhosis in young adults in our cohort suggest that there is a group of “rapid fibroasers” akin to the situation for chronic HCV infection. Conversely, many patients with NASH do not develop significant fibrotic progression over time and can be classified as “slow fibroasers.”

Despite a median follow-up of 5 years (mean, 7 years), the present study failed to reveal a significant difference in survival between NASH cirrhosis and HCV cirrhosis, after controlling for the differences in disease severity at baseline. However, limitations of this study are the small sample size and the fact that it is impossible to ensure that NASH and HCV groups had cirrhosis for the same duration. It is possible that, with a much larger sample size, the trend toward better survival among patients with NASH cirrhosis (Figs. 2 and 3) may have become significant. In this respect, the present results clearly differ from a recent
report of 27 subjects with obesity-related cryptogenic cirrhosis, followed for only (median) 9.3 months, which found that survival was less than that of matched HCV controls.3

Another striking finding of the present study is that no patient with NASH cirrhosis developed HCC. A recent retrospective series of 23 cases of cryptogenic cirrhosis complicated by HCC found that the average length of cirrhosis history before HCC detection was 14 ± 6 years.16 Thus, although the median length of prospective follow-up of NASH-associated cirrhosis in this study (5 years) was the longest reported to date, longer follow-up with larger cohorts may be required to determine the true incidence of HCC. Cirrhosis per se increases the risk of HCC, but there is wide variation in carcinogenic risk depending on disease etiology and the gender ratio of the underlying liver disease.25-27 Recent case reports clearly document that HCC can occur as a complication of NASH-associated cirrhosis.4,5 However, 2 recent large case-control studies indicate that diabetes (a major risk factor for NASH) increases the risk of HCC by 1.3- to 2.4-fold, whereas viral hepatitis increases this risk 13- to 19-fold.28,29 Taken together with these studies, we interpret the present data as indicating that the incidence of HCC is low in NASH cirrhosis. However, given the high prevalence of NASH in the community, the population-attributable risk of NASH to HCC could be considerably higher (13% to 20%).5,29

In conclusion, this prospective, long-term study indicates that liver failure is the most common cause of morbidity and mortality in patients with NASH-associated cirrhosis diagnosed by strict pathologic as well as clinical criteria. HCC appears to be less common in these patients than from cirrhosis owing to hepatitis C. The prognosis of patients with NASH who have developed cirrhosis appears similar to or better than those with HCV-associated cirrhosis.

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