Similarities and Differences in Outcomes of Cirrhosis Due to Nonalcoholic Steatohepatitis and Hepatitis C

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The objective of this study was to prospectively define outcomes of cirrhosis due to nonalcoholic steatohepatitis (NASH) and compare them with those associated with hepatitis C virus (HCV) infection. We compared 152 patients with cirrhosis due to NASH with 150 matched patients with cirrhosis due to HCV. Over 10 years, 29/152 patients with cirrhosis due to NASH died compared with 44/150 patients with HCV ($P < .04$). This was mainly due to the lower mortality rate in patients with Child class A cirrhosis due to NASH versus HCV (3/74 vs. 15/75; $P < .004$). There were no significant across-group differences in mortality in patients with Child class B or C cirrhosis. Sepsis was the most common cause of death in both groups; patients with NASH had a higher cardiac mortality (8/152 vs. 1/150; $P < .03$). Patients with Child class A cirrhosis due to NASH also had a significantly lower risk of decompensation, defined by a 2-point increase in Child-Turcotte-Pugh score ($P < .007$). Cirrhosis due to NASH was associated with a lower rate of development of ascites (14/101 vs. 40/97 patients at risk; $P < .006$). NASH also had a significantly lower risk of development of hepatocellular carcinoma (10/149 vs. 25/147 patients at risk; $P < .01$). In conclusion, compensated cirrhosis due to NASH is associated with a lower mortality rate compared with that due to HCV. It is also associated with a lower rate of development of ascites, hyperbilirubinemia, and hepatocellular carcinoma. However, cardiovascular mortality is greater in patients with NASH. (HEPATOLOGY 2006;43:682-689.)

Nonalcoholic fatty liver disease is one of the most common causes of chronic liver disease in North America.[1-3] It includes both nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH). Approximately 45% and 32% of adults of Hispanic and Caucasian origin, respectively, have hepatic steatosis[4]; it has been estimated that 3% of the population has NASH.[2] NASH can progress to cirrhosis in up to 20% of patients.[5] Age, obesity, severity of insulin resistance, hypertension, and diabetes have all been associated with a higher risk of developing cirrhosis.[6,7] Many patients with cirrhosis due to NASH lose features of steatohepatitis and are categorized as having cryptogenic cirrhosis.[8,9] Approximately 7% to 14% of patients referred for liver transplantation in the United States are known to have NASH or cryptogenic cirrhosis.[10,11]

Although several studies provide data on the natural history of nonalcoholic fatty liver disease,[12-15] only one published study has focused on the natural history of cirrhosis due to NASH.[16] In this study of 23 patients with cirrhosis due to NASH identified from a hospital database, the 10-year survival rate was 84%.[16] Given the small size of this study and the well-preserved liver function in most patients, these data are not easily generalizable to all patients with NASH-related cirrhosis.

In 1992, a prospective study of the natural history of cirrhosis due to varying causes was initiated in the general clinical research center at Virginia Commonwealth University Medical Center. A separate study on the natural history of cirrhosis due to NASH was initiated in 1998 given the increasing numbers of patients seen with this

Abbreviations: NASH, nonalcoholic steatohepatitis; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

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condition. The present study analyzed the outcomes of patients with cirrhosis due to NASH who were enrolled in these two previous studies. The aim of this study was to define the clinical outcomes of cirrhosis due to NASH and compare them with those associated with hepatitis C virus (HCV) infection.

Patients and Methods

This study presents data obtained in a group of 152 patients with NASH and cirrhosis. Data from an age-, sex-, and race-matched population of patients with cirrhosis due to hepatitis C (HCV) who were seen concurrently were used as a control population. All patients provided informed consent to participate in a study examining the natural history of their disease.

Definitions. Cirrhosis was defined by liver histology in all cases. Cirrhosis was attributed to underlying NASH via (1) histological features of steatohepatitis, (2) an absence of clinically significant alcohol consumption (40 gm/wk assessed clinically), and (3) negative tests for alternate causes of cirrhosis. In the presence of cirrhosis, steatosis with varying combinations of cytological ballooning, Mallory bodies and inflammation were used as histological evidence of concurrent NASH.[17,18] With progression toward cirrhosis, central-to-central and central-to-portal bridges develop, distorting the hepatic lobular architecture.[19] Zone III pericellular fibrosis is therefore difficult to define in patients with cirrhosis and was not considered an independent criterion for NASH and cirrhosis. A nurse and a physician independently interviewed each patient and labeled the condition to be "nonalcoholic" if the weekly consumption of alcohol was less than 40 gm.[20] These strict criteria were chosen based on the available literature when the study was initiated and to exclude the confounding effects of moderate alcohol consumption.[20]

In all cases labeled to have cirrhosis due to NASH, the presence of viral hepatitis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, and autoimmune hepatitis were excluded via appropriate studies. Although the presence of a positive antinuclear antibody in low titer ($<$1:160) was not considered an exclusion, those with histological evidence of marked portal hepatitis and piecemeal necrosis were excluded.

Hepatitis C controls were identified on the basis of a biopsy demonstrating cirrhosis and a positive HCV quantitative polymerase chain reaction test in someone who had either not been treated or were virological nonresponders to therapy. These criteria were chosen because sustained virological response to anti-HCV therapy may improve the outcomes of these patients and bias the results.

Patient Identification and Management. Patients with biopsy-proven NASH with cirrhosis, clinical features of cirrhosis with a previous biopsy demonstrating NASH, and suspected cirrhosis due to NASH were enrolled in the study. An attempt to perform a liver biopsy was made in all cases to confirm the diagnosis of cirrhosis and NASH unless the subject refused or there was a contraindication to liver biopsy. This analysis includes those with (1) biopsy evidence of cirrhosis and NASH or (2) an explant showing features of cirrhosis with NASH. Those with cryptogenic cirrhosis were excluded to minimize heterogeneity in the population, though most such patients have underlying NASH.[8,9] The distribution of patients enrolled in each 3-year time frame from 1992-2004 was calculated. For each 3-year time frame, data from consecutive patients with hepatitis C and cirrhosis who matched the age, sex, and Child-Turcotte-Pugh (CTP) scores of the NASH population were used to serve as a control population.

All patients were followed according to standard of care without any experimental therapeutic intervention for NASH. Weight management was performed mainly with diet and exercise. Bariatric surgery was not performed in any subject. As the standard of care changed, the approach to management of cirrhosis was modified accordingly. For example, systematic screening for varices was instituted after publication of the American College of Gastroenterology guidelines.[21] Whereas nonselective beta-blockers remain the mainstay of primary prophylaxis, those with large varices who were intolerant of nadolol have been treated with endoscopic band ligation since 2003.[22] Screening for hepatocellular carcinoma (HCC) was performed once a year until 2000, when it was increased to twice a year with a serum alpha-fetoprotein and ultrasound. In all cases, a rising alpha-fetoprotein level was further assessed via MRI of the liver.

Data Collection, End Points, and Plan of Analysis. The start date for the purposes of analysis was (1) the date of biopsy for those who were asymptomatic at presentation and (2) the date of initial presentation with clinical symptoms of cirrhosis (*e.g.*, ascites for those who were symptomatic at presentation). Patients were followed until they underwent liver transplantation or died. The termination date for analysis was the date of liver transplantation or death. Patients were censored at the time of transplantation or last clinic visit.

The end points examined were survival, development of synthetic failure, varices and variceal hemorrhage, ascites, encephalopathy, and HCC. Time to failure analysis (Kaplan-Meier) was performed, and log-rank analyses were used for across-group comparisons. The impact of baseline risk factors for survival and development of spe-

Table 1. Baseline Demographic, Clinical, and Laboratory Features

Parameter	NASH vs. HCV*			
	Child Class A (n = 74 vs. 75)	Child Class B (n = 43 vs. 42)	Child Class C (n = 35 vs. 32)	*P* (NASH/HCV = 152:150)
Age (yr)	55 vs. 57	52 vs. 52	60 vs. 59	NS
Sex (M)	37 vs. 37	27 vs. 24	10 vs. 13	NS
Caucasian	72 vs. 70	42 vs. 40	32 vs. 32	NS
Body mass index (kg/cm^2)	33.6 vs. 28.3†	34.1 vs. 30.3	34.2 vs. 29.7	.05
Hypertension (n)	35 vs. 28	30 vs. 15†	8 vs. 5	.004
Diabetes (n)	39 vs. 30	28 vs. 20	22 vs. 16	.01
Triglycerides (mg/dL)	210 vs. 176	199 vs. 145†	172 vs. 110†	.003
Cholesterol (mg//dL)	210 vs. 196	175 vs. 165	156 vs. 128†	.03
Bilirubin (mg/dL)	0.9 vs. 0.7	1.1 vs. 1.2	1.9 vs. 1.7	NS
Albumin (gm/dL)	3.7 vs. 3.9	2.9 vs. 2.8	2.5 vs. 2.4	NS
Prothrombin time (s)	10.5 vs. 10.3	12.9 vs. 13.2	13.7 vs. 14.2	NS
AST (IU/L)	95 vs. 145	88 vs. 118	92 vs. 104	NS
ALT (IU/L)	77 vs. 128	55 vs. 117	46 vs. 96	NS
Alkaline phosphatase (IU/L)	129 vs. 118	119 vs. 95	122 vs. 101	NS
Alpha-fetoprotein (ng/dL)	5.1 vs. 6.5	6.1 vs. 5.8	6.6 vs. 6.4	NS
Serum creatinine (mg/dL)	1 vs. 1.1	1.2 vs. 1.3	1.4 vs. 1.3	NS
Child-Turcotte-Pugh score	5.2 vs. 5.5	8.2 vs. 8.4	10.2 vs. 11.3	NS
MELD score	15 vs. 15	18 vs. 18	23 vs. 22	NS
Ascites (n)	3 vs. 5	24 vs. 20	24 vs. 28	NS
Encephalopathy (n)	2 vs. 0	10 vs. 7	15 vs. 10	NS
Variceal hemorrhage (n)	1 vs. 3	6 vs. 5	8 vs. 9	NS
HCC (n)	0 vs. 0	0 vs. 0	3 vs. 3	NS

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma; NS, not significant.

*All values are expressed as the mean.

†$P < .05$.

cific complications were evaluated by logistic regression. The presence of specific categorical features across different subsets was compared using Fisher's exact test. Across-group comparisons of numerical data were performed with ANOVA for normally distributed data, and the Seigel-Tukey test was used for data that were not normally distributed.

Results

From 1992 to October 2004, a total of 245 patients with NASH and clinical and/or histological evidence of cirrhosis were observed. Twenty-six patients either did not have a biopsy (n = 20) or died without a liver biopsy (n = 6). Of the remaining 219 patients, 50 patients had a liver biopsy confirming cirrhosis prior to referral, 63 patients underwent a biopsy that showed cirrhosis, and 39 patients were confirmed to have NASH and cirrhosis in their liver explants. Data from these 152 patients were used for this analysis. Data from a total of 150 HCV controls with cirrhosis were also included.

Baseline Data. At the time of entry, a total of 74 patients with NASH had compensated cirrhosis as defined by a CTP score of less than 7.[23] Baseline demographic, clinical, and laboratory data from patients with cirrhosis due to NASH versus those with HCV are shown in Table 1. As expected, the patients with NASH had a higher prevalence of features of metabolic syndrome (*e.g.*, diabetes, hypertension, and hypertriglyceridemia). The two groups were otherwise comparable with respect to age, sex distribution, race distribution, liver functions, previous history of complications of cirrhosis, CTP scores, and model for end-stage liver disease (MELD) scores.[24,25]

Hepatic steatosis was uniformly present, whereas varying degrees of inflammation were seen in 141/152 cases of NASH. Cytological ballooning was seen in 104/152 cases, whereas Mallory bodies were identified in only 44/152 cases. In the remaining cases, cirrhosis was evident in the liver biopsy or explant in all cases. Only 15 patients had mild stainable iron on their liver biopsy. In patients with HCV, steatosis (grade II or higher) was present in 31/150 cases. Of these, 21 were diabetic and 26/31 had one or more components of the metabolic syndrome.

Mortality. A total of 29 patients with NASH and 44 patients with HCV died ($P = .04$ [Fisher exact test]). This difference was driven mainly by the lower mortality in patients with NASH and compensated cirrhosis compared with patients with HCV (3/74 (4%) versus 15/75 (20%) over a 10-year duration) ($P < .004$ [Fisher exact test]). These data were corroborated by comparison of

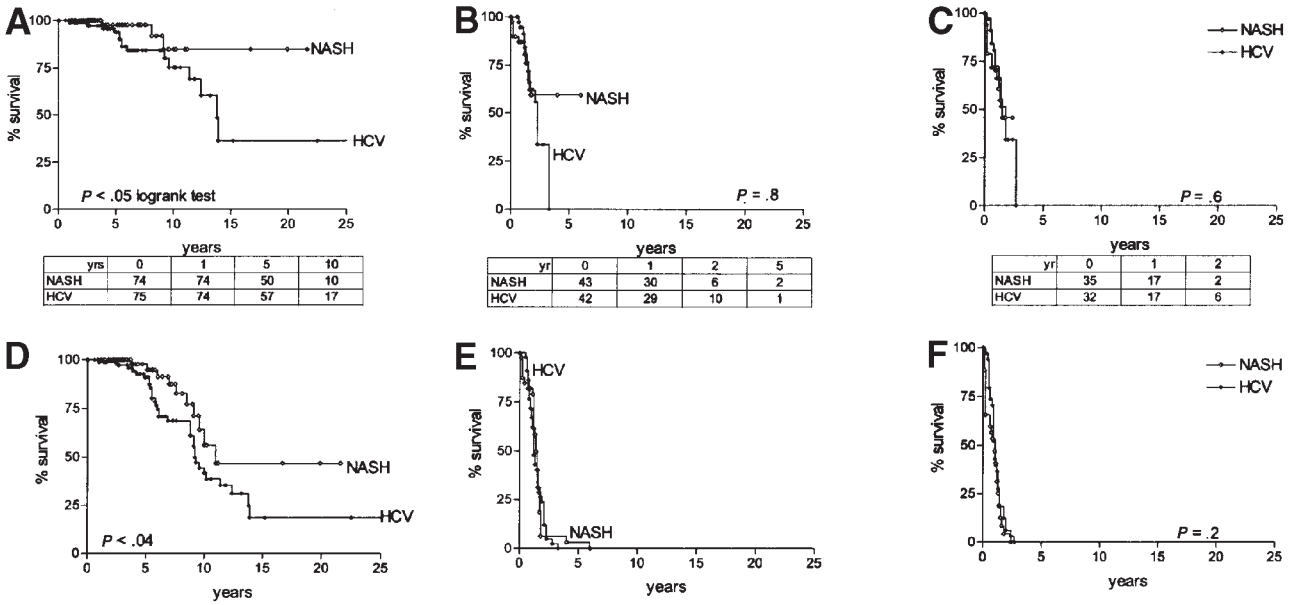

Fig. 1. Long-term hazard of mortality in patients with cirrhosis due to either NASH or HCV. The data are plotted as "time to failure" using the Kaplan-Meier method. Across-group differences in survival were analyzed using the log-rank test. Data from patients with Child class A, B, and C are plotted separately. (A-C) Survival data with patients censored at the time of transplantation (for Child class A, B, and C, respectively). (D-F) Risk of liver-related mortality, which includes both actual deaths and liver transplantations (for Child class A, B, and C, respectively). Patients with Child class A cirrhosis due to NASH had a significantly lower mortality (for both actual (A) and liver-related deaths (D)) compared with patients with HCV. There were no differences in outcomes in patients with Child class B or C cirrhosis due to NASH versus HCV.

survival curves, for both actual and liver-related mortality (death or transplant), of patients with Child class A cirrhosis due to NASH versus HCV ($P < .05$ [log-rank analysis]; OR 3.0 [95% CI 0.96-6.6]) (Fig. 1). There were no significant differences in mortality between the two groups once decompensation set in (Child class B or C). Mortality risks increased with CTP class, as expected, for both NASH and HCV-infected patients ($P < .0001$ by log-rank analysis).

The causes of death are shown in Table 2. Sepsis was the leading cause of death in both groups and was often associated with acute or chronic liver failure. Most cases of fatal infections occurred in the context of ascites, and pneumonia was the most common life-terminating infection in both groups (8/29 vs. 15/44) There were more deaths due to variceal hemorrhage and HCC in patients with HCV, but these differences were not statistically significant. On the other hand, patients with NASH had a significantly higher mortality from heart disease (infarction = 2, congestive heart failure = 6) ($P < .03$ [Fisher exact test]).

Table 2. Causes of Death

Cause of death	NASH (n = 29)	HCV (n = 44)	*P* Value
Infection	12	22	NS
Pancreatitis	1	0	NS
Cholecystitis	0	1	NS
Variceal hemorrhage	5	8	NS
Renal failure	1	4	NS
Hepatocellular cancer	2	8	NS
Heart disease	8*	1	.03

Abbreviation: NS, not significant.
*Two patients who died of heart disease also had HCC.

Age, body mass index, diabetes, serum creatinine, bilirubin, albumin, international normalized ratio, ascites, encephalopathy, and varices were included in a model to predict mortality in patients with NASH. Using the CTP score instead of individual parameters, body mass index and CTP scores (beta coefficients 0.01 ± 0.005 and 0.574 ± 0.001, respectively) independently predicted mortality ($P < .04$ and .0001, respectively). When the CTP score was replaced by the MELD score, body mass index was no longer significant, whereas MELD scores were highly predictive of death (Table 3). This was driven mainly by serum creatinine; virtually all patients with a creatinine level above 2 mg/dL died without a liver transplantation.

A total of 52 patients with NASH and 58 patients with HCV have undergone liver transplantation. The impact of transplantation on survival data were assessed by the hazard of liver-related mortality (transplantation or death) (Fig. 1D-F). The differences in outcomes in patients with Child class A cirrhosis remained, whereas the outcomes of those with more advanced disease remained unchanged.

Table 3. Regression Models for Mortality and Complications of Cirrhosis in Patients With NASH

Model	Beta Coefficient	SE	-2_{log} Likelihood	χ^2	P Value
Mortality			194.33	77.7	.0001
Age	0.002	0.027			.9
Diabetes	−1.05	0.636			.09
BMI	0.008	0.007			.27
Varices	0.045	0.631			.9
MELD	0.327	0.055			.0001
Ascites	1.031	0.779			.2
Encephalopathy	−0.381	0.562			.5
Varices			258.4	41.8	.0001
Age	−0.008	0.016			.6
BMI	−0.007	0.004			.08
Diabetes	0.122	0.361			.7
MELD	0.113	0.035			.001
Ascites	−0.561	0.452			.2
Encephalopathy	0.389	0.392			.3
Platelets	−0.016	0.004			.0001
Ascites			296.8	72.4	.0001
Age	−0.018	0.012			.1
Diabetes	−0.07	0.3			.8
BMI	−0.003	0.003			.4
Varices	−0.346	0.324			.2
MELD	0.186	0.02			.0001
Encephalopathy	1.132	0.357			.001
Encephalopathy			266.1	18.9	.002
Age	−0.01	0.01			.5
Diabetes	0.007	0.35			.9
BMI	0.002	0.003			.5
Varices	−0.461	0.34			.1
MELD	0.108	0.03			.001
Hepatoma			84.53	3.34	
Age	−0.008	0.02			.7
Diabetes	−0.462	0.6			.4
BMI	0.004	0.007			.5
MELD score	0.06	0.04			.15

Abbreviations: BMI, body mass index; MELD, model for end-stage liver disease.

Progression to Liver Failure or Decompensated Cirrhosis. Decompensation was defined by an increase in CTP score of 2 points in patients with Child class A cirrhosis. After 10 years of follow-up, 40% versus 55% of patients with HCV versus NASH remained free of decompensation ($P < .007$ [log-rank test]) (Fig. 2). This was driven partly by a faster rise in total bilirubin and development of ascites in patients with HCV (Fig. 2B). The rates of decline of albumin and increase in international normalized ratio were similar between the two groups (Fig. 2C-D).

Development of Complications of Cirrhosis. For the purposes of this study, the entire cohort of patients with NASH or HCV were considered. Ascites was present in 51 versus 53 patients with NASH and HCV, respectively, at the time of initial evaluation. Of the remaining patients, 14/101 patients with NASH and 40/97 with HCV developed ascites ($P < .006$ [Fisher exact test]). When analyzed as time to failure, these differences remained significant ($P < .03$ [log-rank test]) (Fig. 3). The MELD score (beta coefficient ± SE, 0.186 ± 0.029; $P < .0001$) and presence of encephalopathy (beta coefficient ± SE, 1.132 ± 0.357; $P < .001$) were significantly associated with the time to development of ascites in patients with NASH.

At entry, 72/152 patients with cirrhosis due to NASH versus 77/150 patients with HCV had endoscopic evidence of esophageal varices (Child class A, 29/74 vs. 21/75; CTP class B, 21/43 vs. 30/42; Child class C, 22/35 vs. 26/32). By 4 years, 29 additional patients with NASH and 16 with HCV developed varices (Child class A at entry, 9/45 vs. 10/54; Child class B at entry, 11/22 vs. 4/12; Child class C at entry, 9/13 vs. 2/6). The risk of

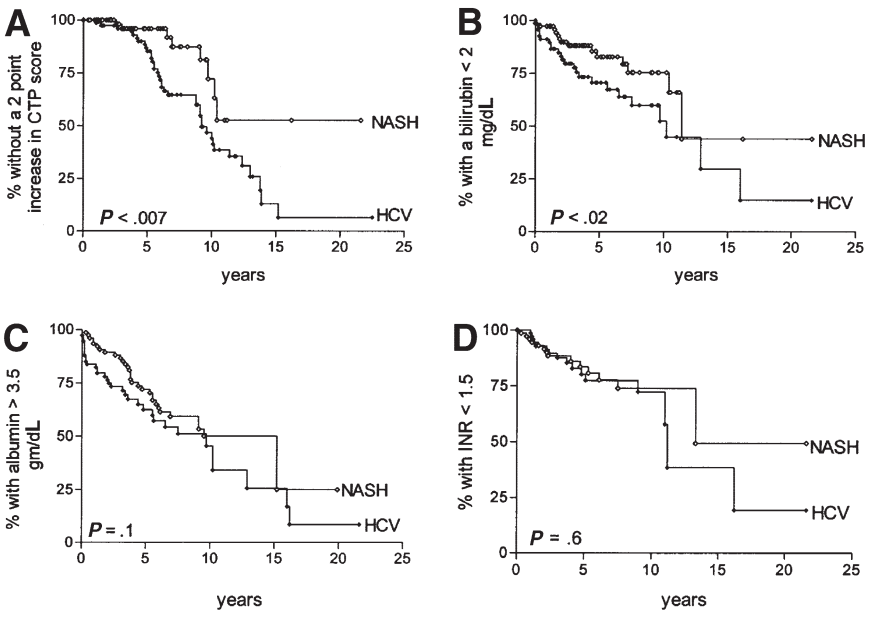

Fig. 2. (A) The long-term risks of decompensation, defined by an increase in CTP score by 2 points, in patients with Child class A cirrhosis in patients with cirrhosis due to NASH versus HCV are shown. (B-D) The risks of worsening (B) serum bilirubin to levels greater than 2 mg/dL, (C) serum albumin to levels less than 3.5 gm/dL, and (D) international normalized ratio greater than 1.5 are also shown. The data are plotted as "time to failure," and across-group differences were analyzed using the log-rank test. Patients with cirrhosis due to NASH had a significantly lower risk of decompensation. This was associated with a lower risk of developing hyperbilirubinemia (B). There were no differences in the risk of developing hypoalbuminemia or hyprothrombinemia. CPT, Child-Turcotte-Pugh.

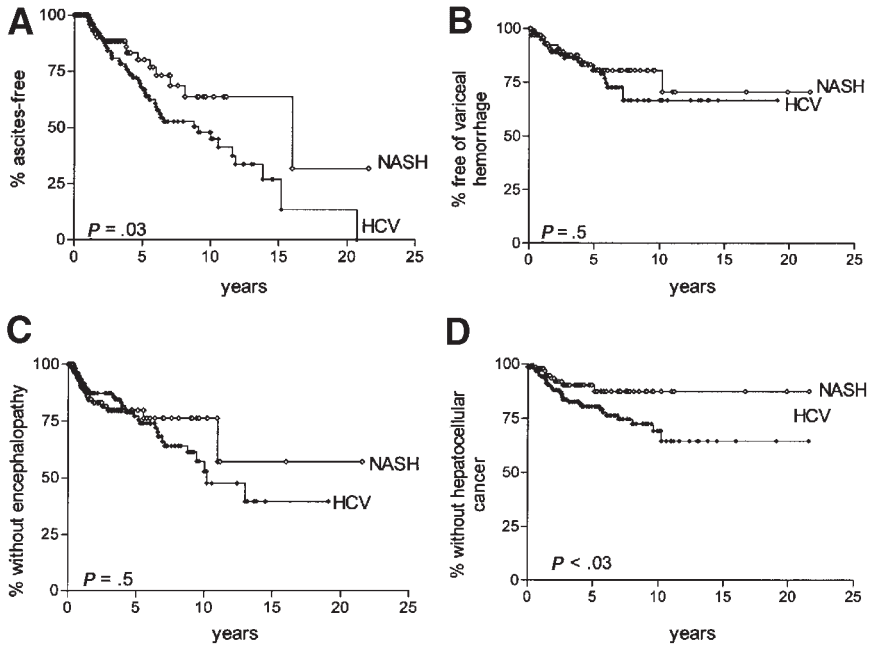

Fig. 3. Long-term risks of developing complications of cirrhosis in patients with cirrhosis due to NASH or HCV. The hazard of developing (A) ascites, (B) variceal hemorrhage, (C) encephalopathy, and (D) HCC are shown as "time to failure" via the Kaplan-Meier method. Across-group differences were analyzed using the log-rank test. Patients with cirrhosis due to NASH had a significantly lower risk of developing ascites and HCC compared with those with hepatitis C.

developing varices over time was inversely related to the platelet count and directly related to the MELD score in patients with NASH (Table 3). Over a 10-year period, 15 versus 17 patients with NASH or HCV, respectively, experienced variceal hemorrhage; of these, 5 and 8 patients from the two groups died (*P* value not significant).

At entry, 27 patients with NASH and 17 patients with HCV had experienced encephalopathy. Over time, 19/125 remaining patients with NASH and 32/133 patients with HCV developed encephalopathy ($P = .16$ [Fisher exact test]). Although this was the second most common complication of cirrhosis, it could be medically managed in practically all cases, and there were no deaths due to encephalopathy in the absence of other complications (*e.g.*, sepsis). The MELD score was strongly associated with the risk of developing encephalopathy (Table 2).

Three patients each with NASH or HCV had HCC at entry. Patients with NASH had a significantly lower risk of development of liver cancer (10/149 vs. 25/147; $P < .01$ [Fisher exact test; hazard ratio based on log-rank 0.48]) (Fig. 3). Six of 10 patients with NASH who developed cancer were diabetic compared with 11/25 patients with HCV. No risk factors for development of HCC could be identified (Table 3).

Discussion

Obesity and the metabolic syndrome are the leading public health problems of our time.[26] An important consequence of the metabolic syndrome is the development of NASH.[27,28] It is estimated that NASH can progress to cirrhosis in up to 20% of patients.[5,13] Given the current epidemic of obesity, particularly in children, it is estimated that the national health care burden related to cirrhosis due to NASH will continue to increase over the next decade.[29,30] Optimal management of these patients will require a clear understanding of the natural history of cirrhosis due to NASH, both with respect to similarities and differences from other causes of cirrhosis. Although the present study confirmed that cirrhosis due to NASH follows a course similar to that of cirrhosis due to other causes, it also identified important differences.

A key finding was that the outcomes of patients with compensated cirrhosis due to NASH were better than those with HCV. It is unlikely that this was due to earlier recognition and referral of patients with cirrhosis due to NASH, because NASH was neither widely recognized nor aggressively looked for in the 1990s. Although earlier development of symptoms could lead to earlier diagnosis in patients with NASH, thereby contributing to bias in the data, the equal frequency of asymptomatic individuals in the two groups contradicts this possibility. However, as with any tertiary care hospital-based study, the potential for referral bias for both NASH and HCV remains.

The mean age of patients with NASH and Child class A cirrhosis was somewhat lower than that of patients with HCV. It is possible that this, along with concomitant alcohol consumption (which was not quantified in patients with HCV), may have contributed to the higher mortality in patients with HCV. The better actual survival of patients with NASH cannot also be attributed to earlier transplantation, because the differences in outcomes were maintained even when liver-related mortality

(death or transplantation) was considered. The lower rate of decompensation of patients with cirrhosis due to NASH corroborates the survival data and supports the concept that the differences in outcomes between those with HCV and NASH were real. These data further corroborate those of Hui et al.[16]

In contrast to the excellent outcomes of patients with compensated cirrhosis, the outcomes of patients with Child class B and C cirrhosis and NASH were poor and were similar to those noted for HCV. Such patients often had complications and comorbidities that negatively affected the ability to quickly list them for transplantation or keep them alive until an organ became available. On the other hand, patients with Child class A cirrhosis that progressed to more advanced cirrhosis were listed expeditiously for transplantation. This underscores the need for early referral of patients with cirrhosis to transplantation centers.

The present study also demonstrates that, as with other causes of cirrhosis,[31] ascites is the most common complication of cirrhosis. However, the risk of developing ascites is significantly lower in patients with NASH than in patients with hepatitis C, another common and important cause of cirrhosis.

The current study further confirms and corroborates existing literature regarding the clinical importance of infections in the outcomes of patients with cirrhosis in general.[32-34] In this study, death occurred most commonly due to sepsis and multiorgan failure associated with ascites. Although ascites did not directly cause death, ascites-related complications (particularly pneumonia and spontaneous bacterial peritonitis with renal insufficiency) contributed substantially to mortality. Thus, while substantial strides have been made in the improvement of outcomes related to variceal hemorrhage, which are corroborated in this study as well,[35] ascites continues to contribute substantially to mortality in patients with cirrhosis.

It is also noteworthy—though not unexpected—that heart disease contributed disproportionately to mortality in patients with cirrhosis due to NASH. Nonalcoholic fatty liver disease has been associated with impaired endothelial function and carotid intimal thickness.[36,37] This group of patients had a significantly higher prevalence of risk factors for coronary heart disease and congestive heart failure (*e.g.*, hypertension, diabetes, and hyperlipidemia) compared with those with HCV. However, one must be cognizant of the possibility that patients with HCV and symptomatic heart disease may not have been referred for tertiary liver care.

Another important finding is the significantly lower risk of HCC in patients with NASH and cirrhosis compared with HCV. Although numerous reports of HCC in patients with NASH exist,[38-42] most studies report those with cancer (*i.e.*, the numerator) and do not provide data on the population at risk (*i.e.*, the denominator). The current report is the largest prospective study of the natural history of cirrhosis due to NASH to date with over 10 years of follow-up using a predefined screening protocol for HCC both in patients with NASH and in patients with HCV. This study demonstrates that the risk of liver cancer in patients with cirrhosis due to NASH is lower than in those with HCV but is not nonexistent, as noted in the study by Hui et al.[16]

Case–control studies have found a higher prevalence of features of nonalcoholic fatty liver disease in patients with HCC associated with cryptogenic cirrhosis than other causes of cirrhosis.[43] Retrospective studies have also reported that cryptogenic cirrhosis is the second most common liver disease associated with liver cancer.[44] It should be noted that our study did not evaluate cryptogenic cirrhosis, which may represent a more advanced stage of the disease and may have a different risk for liver cancer than those with cirrhosis and histological evidence of NASH.

In summary, the survival of patients with cirrhosis due to NASH decreases markedly once decompensation occurs. Ascites is the most common complication and contributes substantially to mortality. The onset of renal failure is the strongest predictor of mortality. HCC occurs in patients with NASH-related cirrhosis, but the rate of development is lower than that reported in the literature for cirrhosis due to hepatitis C. These data are likely to be important in the design of future therapeutic interventions in this patient population and also in the everyday management of such patients in clinical practice.

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