NAFLD May Be a Common Underlying Liver Disease in Patients With Hepatocellular Carcinoma in the United States

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The incidence of hepatocellular carcinoma (HCC) in the United States is increasing, but the clinical characteristics of American patients with HCC have not been well described. The aims of this study were to determine the etiology of liver disease and short-term outcome among HCC patients presenting to a single center in the United States. One hundred five consecutive patients with HCC were studied; mean age was 59 years, 67% were men, and 76% were non-Hispanic white. The most common etiology of liver disease was hepatitis C (51%) and cryptogenic cirrhosis (29%). Half of the patients with cryptogenic cirrhosis had histologic or clinical features associated with nonalcoholic fatty liver disease (NAFLD). Fifty-three (50%) patients had HCC detected during surveillance (group I), whereas the remaining patients had symptomatic tumors (group II). Group I patients had smaller tumors ($P = .01$), were more likely to be eligible for surgical treatment ($P = .005$), and had a better median survival compared with patients in group II ($P = .001$). Patients with cryptogenic cirrhosis were less likely to have undergone HCC surveillance and had larger tumors at diagnosis. In conclusion, hepatitis C and cryptogenic liver disease are the most common etiologies of diseases in our patients with HCC. NAFLD accounted for at least 13% of the cases. Patients who underwent surveillance had smaller tumors and were more likely to be candidates for surgical or local ablative therapies. Because of the increasing incidence of NAFLD, further studies are needed to determine the risk of HCC in patients with NAFLD. (HEPATOLOGY 2002;36:1349-1354.)

Hepatocellular carcinoma (HCC) was formerly considered an uncommon malignancy in the United States. Intrahepatic liver cancer (combination of HCC and cholangiocarcinoma) ranked as the 8th most common malignancy in the United States from 1973 to 1980, accounting for 1 death per 100,000.[1] However, 3 national databases (NCI Surveillance Epidemiology and End Results database, United States vital statistics, and Department of Veteran Administration) found that the incidence of HCC in the United States has been increasing over the last decade.[2] In 1998, intrahepatic liver cancer ranked as the 6th most common malignancy in the United States, resulting in a death rate of 3.5 per 100,000.[1] Much of the increase in intrahepatic liver cancer is related to an increase in the incidence of HCC. The increase in incidence of HCC in the United States has been attributed to the hepatitis C virus (HCV) epidemic, but data on the prevalence of HCV infection among patients with HCC in the United States are not available. Recently, nonalcoholic fatty liver disease (NAFLD) has been recognized to be one of the most common causes of chronic liver disease in the United States.[3] Several studies have demonstrated that NAFLD may progress to cirrhosis.[4-6] In addition, recent studies found that a high percentage of patients who underwent liver transplantation for cryptogenic cirrhosis probably had NAFLD, indicating that NAFLD may be an important cause of end-stage liver disease.[7-9] A study from Italy also reported an association between NAFLD and HCC.[10]

Survival of patients with HCC has improved minimally over the last 2 decades, with 1-year survival rate

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; AFP, α-fetoprotein; NASH, nonalcoholic steatohepatitis.

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increasing from 14% in 1977 to 1981 to 23% in 1992 to 1996, whereas the 5-year survival rate rose from 2% to 5%.[11] These disappointing results were observed despite dramatic improvements in the survival of patients with other malignancies such as breast or colon cancer during the same time period. Several prospective studies have found that surveillance of high-risk individuals can increase the rate of detection of early HCC.[12-15] However, these studies have shown minimal or no improvement in overall survival. Because only 13% of patients with HCC are eligible for liver transplantation or surgical resection,[16] limited options for curative treatment have further dampened the enthusiasm for HCC surveillance. It is unknown what percentage of patients with HCC in the United States is detected by surveillance.

The aims of this prospective study were to determine the etiology of liver disease and tumor staging at diagnosis among HCC patients presenting to a single referral center in the United States. In addition, we determined whether patients whose tumor was detected via surveillance were more likely to be candidates for surgical therapy than patients presenting with clinical symptoms. The results in our cohort of 105 consecutive HCC patients form the basis of this report.

Patients and Methods

Patients and Etiology. A database of all patients with a diagnosis of HCC was established in January, 2000, at the University of Michigan Medical Center per local Institutional Review Board guidelines. Written informed consent was obtained from each patient. The diagnostic criteria of HCC was based on liver histology, and, in the absence of histology, an AFP >200 ng/mL with a hypervascular mass on triple-phase computerized tomography (CT) scan or magnetic resonance imaging (MRI). The age at diagnosis, gender, ethnicity, body mass index (BMI), estimated duration from diagnosis of liver disease to diagnosis of HCC, Child-Turcotte-Pugh (CTP) score, serum α-fetoprotein (AFP), and tumor size and location were recorded.

Etiology of underlying liver disease was attributed to HCV based on detection of hepatitis C antibody/HCV RNA in serum, hepatitis B (HBV) [hepatitis B surface antigen (HBsAg)] in serum, alcohol (daily alcohol intake more than 30 gm/ethanol per day for more than 15 years), hereditary hemochromatosis (HH) (positive genetic testing or hepatic iron index >1.9), primary biliary cirrhosis (PBC) (serum antimitochondrial antibody and compatible histology), primary sclerosing cholangitis (PSC) (beading on cholangiogram), autoimmune hepatitis based on the revised scoring system, and α-1 antitrypsin deficiency (phenotypic analysis). The etiology of liver disease was considered to be cryptogenic if no cause was identified after exhaustive testing as described above. The presence or absence of cirrhosis was determined based on histologic assessment of non-neoplastic liver tissue. A diagnosis of diabetes was made based on the American Diabetes Association criteria.[17] Hypercholesterolemia was defined as a serum cholesterol of >200 mg/dL and hypertriglyceridemia as serum triglyceride level of >200 mg/dL.[10] Portal hypertension was defined as evidence of hypersplenism, history of esophagogastic varices, presence of ascites, or hepatic encephalopathy.

Surveillance. Patients with a diagnosis of HCC were divided into 2 groups for analysis. Group I (n = 53) patients had detection of HCC during surveillance. Surveillance included ultrasound of the liver and AFP testing every 6 to 12 months over a period of at least 12 months prior to diagnosis of HCC. In our institution, all patients with cirrhosis, regardless of the etiology of liver disease, undergo surveillance with ultrasound of the liver and AFP every 6 to 12 months. Eleven patients underwent tumor surveillance at other institutions and were referred to us after HCC was diagnosed. Patients with AFP levels >20 ng/mL or a solid liver mass on ultrasound were further evaluated by triple-phase CT or dynamic contrast-enhanced MRI. Group II (n = 52) patients presented with clinical symptoms of abdominal pain, discomfort, nausea, or weight loss that led to evaluation and diagnosis of HCC.

Treatment Strategies. All patients were assessed for possible liver transplantation or surgical resection. Transplant eligibility was defined as a single tumor lesion <5 cm in maximal diameter or 3 lesions each <3 cm in maximal diameter without portal vein infiltration or extrahepatic metastasis.[18] Surgical resection eligibility was defined as a single tumor lesion involving 1 hepatic lobe without portal vein infiltration or extrahepatic metastasis and Child class A. Percutaneous radio frequency thermal ablation of HCC is the preferred local ablative therapy in our center.

Statistical Analysis. Data were analyzed with Student's t test for comparison of means and χ^2 test with Yate's correction and Fisher exact test for categorical variables using SAS (Cary, NC). P values < .05 were considered statistically significant.

Results

A total of 163 patients with liver masses and liver disease were seen in the Liver Clinic at the University of Michigan over a 24-month period. Of these, 105 (64%) patients were diagnosed with HCC. The diagnoses in the remaining 58 patients included 16 dysplastic nodules, 14

Table 1. Demographic and Clinical Data of 105 Patients With HCC

Age (yr)	59.3 ± 22.5
Gender (male:female)	70:35
Ethnicity, n (%)	
Non-Hispanic white	80 (76)
African American	13 (12)
Asian	5 (5)
Hispanic	3 (3)
Unknown	4 (4)
Etiology, n (%)	
HCV	41 (39)
Cryptogenic	30 (29)
HCV + alcohol	13 (12)
Alcohol	11 (10)
HBV	6 (6)
Other*	4 (4)
Laboratory data	
Bilirubin (mg/dL)	2.6 ± 3.4
INR	1.2 ± 0.3
Albumin (g/dL)	3.1 ± 0.5
Platelet (k/mm^3)	109 ± 61
AFP (ng/mL)	14,856 ± 16,523
CTP score	7.3 ± 1.7
% Child's A	47
% Child's B	38
% Child's C	15
PST† 0/1/2	57/35/13

NOTE. All data presented as mean ± standard deviation.

Abbreviations: HCV, hepatitis C; HBV, hepatitis B; INR, international normalized ratio.

*Includes hemochromatosis, autoimmune hepatitis, and primary biliary cirrhosis.

†Performance status test by the ECOG score.

hemangiomas, 3 cholangiocarcinomas, 9 hepatic cysts, 5 adenomas, 5 focal nodular hyperplasia, and 6 metastatic liver masses. The diagnosis of HCC was made based on histology in 76 (72%) patients and a combination of AFP and imaging in the other 29 (28%) patients. Table 1 summarizes the demographic and clinical data of these 105 patients. All 105 patients had chronic liver disease, 90% had biopsy specimen-proven or clinical suspicion of cirrhosis. Overall, 31% of patients had AFP levels <20 ng/mL, and only 35% had AFP levels >200 ng/mL at diagnosis. There was no relationship between AFP levels and etiologies of underlying liver disease ($P = .563$).

Of the 105 patients with HCC, 62 (59%) received treatment. Of these, 11 (10%) underwent orthotopic liver transplantation, whereas 5 (4%) patients underwent surgical resection of the tumor. Twenty-two (21%) patients underwent percutaneous radio frequency thermal ablation, 11 (10%) received systemic chemotherapy, 12 (11%) received experimental antiangiogenesis therapy, and 1 received transarterial chemoembolization as the primary method of treatment. A total of 33 (31%) patients died during a mean follow-up of 12.4 months (range 1 to 25 months).

Hepatitis C was the leading etiology of underlying liver disease among the patients with HCC (51%). Cryptogenic liver disease was the second most common diagnosis (29%). Compared with patients with other causes of liver disease, patients with cryptogenic disease were more likely to be women (60% vs. 28%, $P = .001$) and to have BMI ≥ 30 (58% vs. 25%, $P = .02$) (Table 2). Six (20%) patients in the cryptogenic liver disease group had evidence of nonalcoholic steatohepatitis (NASH), and all 6 had steatosis, lobular inflammation, ballooning degeneration, and sinusoidal fibrosis[19] on liver biopsy 4.3 ± 1.6 years prior to the diagnosis of HCC. All biopsy specimens were reviewed by a single pathologist in our institution who was unaware that these patients subsequently developed HCC. Eight additional patients had clinical features commonly associated with NAFLD, including a BMI ≥ 30, history of diabetes mellitus, hypertriglyceridemia, and female gender.[6,20] Of the 14 patients with prior histologic diagnosis of NASH or clinically suspected NAFLD, all had cirrhosis in the adjacent non-neoplastic liver at the time of HCC diagnosis, with only 3 having more than 30% steatosis in the nonneoplastic liver tissue. Patients suspected of having NAFLD were significantly more obese (BMI ≥ 30 in 93% vs. 12.5%, $P < .001$), diabetic (93% vs. 25%, $P < .001$), and hyperlipidemic (29% vs. 6%, $P < .001$) than the other patients with cryptogenic cirrhosis. There was no significant difference in gender, tumor size, and percentage with HCC surveillance between these 2 groups. Patients with cryptogenic cirrhosis as the underlying liver disease were less likely to have undergone HCC surveillance (23% vs. 61%, $P = .01$). This resulted in larger tumors at diagnosis (7.6 vs. 4.4 cm, $P = .03$), and a lower proportion of patients eligible for surgical (3 underwent resection, 1 placed on transplant waiting list) or local ablation therapy (5 had radio fre-

Table 2. Comparison of HCC Patients With Cryptogenic Cirrhosis Versus Other Etiologies

	Cryptogenic (n = 30)	Other Etiologies (n = 75)	P Value
Female (%)	60	28	.001
Mean age ± SD (yr)	57 ± 16	62 ± 13	>.05
Non-Hispanic white (%)	90	72	>.05
BMI >30 (%)	58	25	.02
Diabetes (%)	47	8	.006
Hypertriglyceridemia (%)	16	2	.001
Hypercholesterolemia (%)	13	2	.07
Maximal tumor diameter mean ± SD (cm)	7.6 ± 6	4.4 ± 5	.03
AFP <20 ng/mL (%)	27	30	>.05
Detected by surveillance (%)	23	61	.01

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index.

Table 3. Characteristics of HCC Patients Detected by Surveillance (Group I) and Those With Clinical Symptoms (Group II)

	Group I Surveillance (n = 53)	Group II Symptomatic (n = 52)	P Value
Age (yr)	58.3 ± 10.7	61.4 ± 12.7	>.05
Gender (male:female)	37:16	33:19	>.05
Ethnicity (%)			
Non-Hispanic white	86	87	>.05
African American	6	8	>.05
Asian	4	1	>.05
Hispanic	1	3	>.05
Unknown	3	1	>.05
Etiology of liver disease (%)			
HCV	62	38	>.05
Cryptogenic	11	46	.005
Alcohol	10	12	>.05
HBV	10	2	>.05
Other	7	2	>.05
Child class (%)			
A	35	43	>.05
B	44	42	>.05
C	21	10	>.05
AFP, ng/mL (%)			
<20	42	19	.001
20-200	38	25	>.05
>200	19	56	<.001
Maximal tumor diameter (cm)	3.7 ± 2.1	7.6 ± 4.9	.01
% <3 cm	38	18	.02
% 3-5 cm	35	14	.01
% >5 cm	27	69	<.001
No. of tumor lesions (%)			
1	48	40	>.05
2	12	17	>.05
3	15	6	>.05
>3	21	29	>.05
Diffuse	4	8	>.05
Lobar distribution (unilobar bilobar)	38/15	28/24	>.05
Portal vein invasion (%)	32	38	>.05
Extrahepatic metastasis (%)	7	15	.09
Treatment (%)			
Untreated	30	52	.01
Eligible for transplant	35	10	.001
Underwent liver transplantation	19	2	.01
Surgical resection	4	6	>.05
Radiofrequency ablation	34	11	.01
Survival (%)	72	65	.15

NOTE. Data presented as mean ± standard deviation.

quency ablation). During follow-up, 11 (37%) patients with cryptogenic liver disease died.

There was no difference in age, gender, ethnicity, and Child class between group I and II patients (Table 3). Compared with patients who had symptomatic HCC (group II), surveillance patients (group I) had smaller tumors at diagnosis, with a mean maximal diameter of 3.7 ± 2.1 cm vs. 7.6 ± 4.9 cm ($P = .01$). However, there was no difference in the number of tumor nodules, presence of portal vein invasion, and distant metastasis. Almost half, 42%, of the group I patients had AFP levels <20 ng/mL at diagnosis, compared with 19% in the group II patients ($P = .001$).

Patients whose tumors were detected by surveillance were more likely to be candidates for surgical or local ablative therapy. Twenty (35%) group I patients were eligible for liver transplantation or surgical resection, compared with only 5 (10%) group II patients ($P = .001$). Of these, 12 patients in group I underwent surgical therapy (10 liver transplantations and 2 resections), compared with 4 in group II (1 transplantation and 3 resections) ($P = .01$). Eighteen (34%) group I versus 6 (12%) group II patients underwent local therapy with radio frequency ablation ($P = .01$). Compared with group II, group I patients had a significantly improved median survival (19 vs. 5 months, $P = .001$).

Discussion

In this case series of 105 consecutive patients with HCC presenting to a tertiary center in the United States, we confirmed that HCV is the most common underlying liver disease. Nevertheless, HCV only accounted for 51% of our cases, with cryptogenic liver disease accounting for 29% of cases. Compared with patients with other causes of liver disease, patients with cryptogenic cirrhosis and HCC were more often women and obese. Approximately 50% of the patients with cryptogenic liver disease had a prior histologic diagnosis of NASH or clinical features associated with NAFLD. Our data suggest that the underlying liver disease in 13% of our patients with HCC may be due to NAFLD. Progression from NASH to HCC has been reported in 1 female patient after 10 years of follow-up.[21] In a recent series from Italy, 23/641 (4%) of patients with HCC were thought to have NAFLD as the cause of their liver disease.[10] Because steatosis may decrease as NAFLD progresses and not all patients with NAFLD are women, obese, diabetic, or hyperlipidemic, the proportion of patients with NAFLD as the underlying liver disease among our HCC patients may even be higher.[5,6,22] In view of the increasing prevalence of NAFLD in the United States, larger prospective studies are necessary to confirm the etiologic association between NAFLD and HCC. Our observation has 2 important implications. First, the incidence of HCC in the United States may continue to increase even after the consequences of the HCV epidemic have leveled off. Second, and more importantly, we found that patients with cryptogenic liver disease were less likely to be enrolled in HCC surveillance programs resulting in delay in diagnosis. This may be due to an underappreciation of the risk of HCC in these patients, compared with patients with viral hepatitis.[23,24]

Our data have several limitations. Although our findings suggest that NAFLD is a common cause of the underlying liver disease in our patients with HCC, a prospective study of patients with NASH is necessary to confirm the etiologic association and to determine the risk of developing HCC in this population. Another limitation is that our data may not be representative of other regions in the United States. Michigan has a high prevalence of obesity; 53% of the residents have BMI $>$ 30. Despite these limitations, we believe that NAFLD may be an important cause of cryptogenic cirrhosis as well as HCC in the United States.

Fifty percent of our patients had their tumors detected during surveillance. Patients who underwent surveillance had smaller tumors at diagnosis and were more likely to be eligible for surgical or local ablative therapies. In addition, there was a significant improvement in survival among those who underwent tumor surveillance. Our data support previous findings that surveillance of patients with cirrhosis using AFP and ultrasound can lead to early diagnosis of HCC.[13-15,25] We recognize that the 2 groups of patients were not randomized, and improved survival in group I patients may be related to lead-time bias. Nevertheless, our data corroborate previous studies indicating that surveillance may increase the rate of early detection and eligibility for curative therapies, which may in turn translate into improved survival.

Although the patients who underwent surveillance had smaller tumors, half of them had more than 1 tumor, and a third had portal vein invasion at diagnosis. The high proportion of patients with advanced tumors despite surveillance may be related to the heterogeneity in frequency of surveillance (every 6-12 months) performed by a diverse group of hepatologists. Even though HCC surveillance is usually performed at 6-month intervals, prior prospective studies have used varying intervals from 6 to 12 months.[26] We have recently implemented a stricter HCC surveillance program to determine whether we can improve our early detection rate. Our disappointing results with surveillance may also be related to the insensitivity of AFP in the early detection of HCC. Thus, 42% of group I patients had normal AFP levels at diagnosis, and only 19% had AFP levels $>$200 ng/mL. Because accuracy of ultrasound is dependent on operator skill and experience,[27] more sensitive serum markers for HCC are needed to improve the results of HCC surveillance programs. Preliminary results of an ongoing study in our center found that des-γ carboxy prothrombin is a more sensitive marker in the detection of HCC than AFP.[28]

In summary, we have reported the first large case series of HCC patients in the United States. We found that, in addition to HCV, NAFLD is a common underlying liver disease in American patients with HCC. Prospective studies in patients with NASH will help determine the true incidence of HCC in this population. Because of the increasing prevalence of NAFLD, the incidence of HCC in the United States may continue to increase even after the consequences of the HCV epidemic have leveled off. Patients who underwent surveillance had smaller tumors at diagnosis and were more likely to be candidates for surgical or local ablative therapies. Although the 2 groups of patients in our series were not randomized, our findings suggest that surveillance of patients with cirrhosis can detect HCC at an earlier stage, possibly leading to an improved survival. Because of the low sensitivity of AFP, more reliable serum markers for HCC are needed to improve the results of surveillance programs.

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