Original Paper

Clinical Characteristics of Patients with Cryptogenic Hepatocellular Carcinoma in a Hepatitis B Virus-Endemic Area

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Key Words

Anti-HBc antibodies · Cryptogenic · Hepatocellular carcinoma · Non-alcoholic fatty liver disease · Non-B non-C non-alcohol

Abstract

Objectives: Chronic hepatitis B virus (HBV) infection is the most common cause of hepatocellular carcinoma (HCC) in South Korea, but a high prevalence of metabolic diseases may result in increases in the incidence of cryptogenic HCC (cHCC). We studied characteristics of the cHCC in a single-center cohort. ***Methods:*** A cohort of 1,784 HCC patients newly diagnosed and treated at the National Cancer Center, Korea, between 2004 and 2009 was reviewed and analyzed. ***Results:*** The cause of HCC was categorized as cHCC, HBV, hepatitis C virus (HCV), or alcohol. Overall, 162 (9.1%) patients of the HCC cohort had cHCC, and their mean age was 61.9 years. The median survival of cHCC patients was 24.7 months, which was the second shortest among the four groups after HBV HCC. cHCC patients had the largest tumor size (mean 7.4 cm) and the second highest proportion of poor prognostic factors such as the proportion of poorly defined tumors and extrahepatic spread in imaging studies. cHCC patients had better survival than HBV HCC patients according to multivariate analysis. Among cHCC patients, 137 (84.6%) had anti-HBc IgG antibodies, but this sub-group had different clinical features to those of HBV HCC patients. The body mass index (BMI) and hyperglycemia and hypercholesterolemia levels in cHCC patients were similar to those in HCV and alcoholic HCC patients. ***Conclusions:*** Anti-HBc IgG antibodies were present in most cHCC patients, but cHCC patients had better survival than HBV HCC patients on multivariate analysis. However,

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cHCC patients had a larger mean tumor size and more aggressive tumor characteristics than HCV HCC or alcoholic HCC patients did. It is hoped that this study will contribute to a better understanding of cHCC in HBV-endemic areas.

Introduction

Hepatocellular carcinoma (HCC) may result from liver cirrhosis of various causes, including hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, chronic alcohol consumption [1, 2], non-alcoholic fatty liver disease (NAFLD) [3–8], and unknown causes [9]. Although the incidence of HCC varies in different localities, HBV and HCV infections are the most common causes of HCC [10]. However, HBV vaccination programs and the prevention of iatrogenic infections (such as HCV screening of transfused blood) have reduced the incidence of HCC of viral causes, whereas the proportion of HCC of non-viral cause has, as a result, relatively increased [11]. The majority of (cHCC) cases in the United States are caused by NAFLD, a hepatic manifestation of the metabolic syndrome [12]. NAFLD-associated HCC accounts for more than half of patients with non-HBV, non-HCV, non-alcoholic (NBNCNA) cHCC cases in some reports [5, 13]. Because the proportion of the population with metabolic syndrome has increased, NAFLD has also increased recently in Asian as it has in Western countries [14], and now it is present in 5%–40% of the general population [15, 16]. NAFLD can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and HCC [3–7]. In the United States, among patients older than 60 years, NAFLD appears to be responsible for as much HCC as HCV is [17].

There are a few reports on the characteristics of cirrhosis according to cause [18–20]; however, such comparative studies of HCC are rare [4, 21]. In South Korea, the incidence of cryptogenic, or NBNCNA, HCC has reportedly increased from 2.3% to 12.2% [21–24]. Therefore, there is a need for better understanding of cHCC. In this cohort study, we examined the clinical characteristics, metabolic factors, and prognostic factors in patients with cHCC compared with those with HCC from other causes in a HBV-endemic area.

Materials and Methods

Patients and Classification of HCC According to Cause

A cohort of 1,972 patients newly diagnosed with HCC and treated at the National Cancer Center hospital, Korea, between January 2004 and December 2009 was investigated for this study [25]. The patients were enrolled prospectively, and relevant clinical data and tumor characteristics were extracted retrospectively from their medical records. The patients were followed up until March 2012. HCC was diagnosed on the basis of the guidelines of the Korea Liver Cancer Study Group/NCC, Korea [26, 27]. A total of 185 patients with inadequate or missing metabolic values and 3 rare cases (one case each of Budd-Chiari syndrome, primary biliary cirrhosis, and autoimmune hepatitis) were excluded, and so 1,784 HCC patients were finally enrolled in this study.

In HCC patients with positive HBsAg or anti-HCV test results, HBV or HCV infection, respectively, was considered to be the cause of HCC (HBV HCC and HCV HCC, respectively), regardless of any history of alcohol consumption. Serum HBsAg and anti-HCV were determined with chemiluminescent immunoassays using an Architect HBsAg QT (Abbott Laboratories, Abbott Park, IL, USA) and Advia Centour XP Immunoassay system and Advia Centaur HCV (Siemens, Germany) assays. HCC patients who were negative for both HBsAg and anti-HCV, but had a history of chronic alcohol abuse, were classified as alcoholic HCC. The history of chronic alcohol abuse was checked by a review of medical records, including questionnaires. HCC patients who were negative for HBsAg and anti-HCV and who had no history of chronic alcohol abuse were classified as having cHCC.

23

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Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

We defined cHCC as NBNCNA HCC, but many of the cHCC patients might have had a past infection with HBV. Even though HBsAg appeared negative, the existence of anti-HBc from an occult or past infection might have influenced the characteristics of HCC [28]. Therefore, we performed additional subanalyses according to the presence of anti-HBc antibody in cHCC patients. Moreover, the presence of fatty liver, which is one of the crucial findings of cHCC, was determined with imaging studies using ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI).

Variables Analyzed

The Modified Union for International Cancer Control (mUICC) stages were used for tumor staging [29], and the Barcelona Clinic for Liver Cancer (BCLC) staging system was used for clinical staging [30]. The Child–Pugh and Model for End-stage Liver Disease (MELD) scoring systems were used for clinical diagnosis and classification of the severity of liver dysfunction [31]. The tumor type (i.e., well or poorly defined HCC), the presence of cirrhosis or fatty liver, portal vein thrombosis, and extrahepatic spread were confirmed by initial CT imaging studies at the first visit. Additionally, to establish the severity of liver fibrosis, we measured platelet counts and the aspartate aminotransferase to platelet ratio (APRI), an index that reflects liver fibrosis [13, 32].

We retrospectively analyzed survival, tumor stage, and characteristics that might affect the prognosis of HCC patients according to cause. We also compared the initial treatments, which included liver transplantation, radiofrequency ablation therapy (RFA), liver resection, conventional transarterial chemoembolization (cTACE) therapy, external beam radiation therapy, systemic cytotoxic chemotherapy, sorafenib (molecular-targeted therapy), and conservative management.

In addition, we reviewed the clinical records of HCC patients with respect to clinical and laboratory variables such as body mass index (BMI), blood pressure, fasting glucose values, total serum cholesterol values, and liver function tests [such as serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. We also checked for fatty liver in the initial CT imaging studies.

Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at first visit or a previous diagnosis of hypertension. Hyperglycemia was defined as fasting glucose level >126 mg/dL [33] or a previous diagnosis of diabetes mellitus (DM). Hypercholesterolemia was defined as total cholesterol >240 mg/dL [34]. The study protocol was approved by the Institutional Review Board of the National Cancer Center, Korea [NCCNCS-13–821].

Statistical Analyses

The Kaplan–Meier method and the Cox proportional hazard model were used for survival analysis. Chi-square tests were employed to compare categorical variables. Independent t-tests were used to define whether there was a statistically significant difference between the means in two unrelated groups. For variables not following a normal distribution (e.g., ASL/ALT), an analysis of variance test was also performed. All statistical analyses were performed with STATA version 10.0 (Stata Corp, College Station, TX, USA), and values of $p < 0.05$ were considered statistically significant.

Results

Survival and Clinicopathologic Characteristics

A total of 1,784 HCC patients were classified according to the cause of HCC. The number of cases of cHCC, HBV HCC, HCV HCC, and alcoholic HCC were 162 (9.2%), 1,320 (74.0%), 167 (9.4%), and 135 (7.5%), respectively. Comparisons of overall survival and clinicopathologic characteristics between cHCC patients and patients with HCC due to other causes are presented in tables 1, 2 and fig. 1. The 1-year, 3-year, and 5-year survival rates of cHCC were 61.7%, 42.2%, and 35.3%, respectively, and no significant differences were found between these survival rates and those of HBV HCC, HCV HCC, or alcoholic HCC (fig. 1). Median survival was 24.7 months for cHCC, which was the second shortest after that of HBV HCC (18.6 months). cHCC patients [hazard ratio (HR)=1] had better survival than HBV HCC patients (HR=1.251) on multivariate analysis (table 2).

The mean age at diagnosis of cHCC patients (61.9 years) was less than that for HCV HCC patients (66.1 years) and greater than that for HBV HCC patients (53.7 years) (both p<0.001).

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 1. Survival and clinicopathologic characteristics of 1,784 HCC patients, with comparisons between cHCC and that from other causes

Characteristics (n=1,784)		Cause of HCC				cHCC		
		Cryptogenic (n=162) (9.1%)	HBV (n=1,320) (74.0%)	HCV (n=167) (9.4%)	Alcohol (n=135) (7.5%)	vs. HBV p value	vs. HCV p value	vs. Alcohol p value
Survival	1 YSR	61.70%	57.50%	72.50%	75.60%	0.23	0.67	0.302
	3 YSR	42.20%	38.30%	44.60%	47.00%			
	5 YSR	35.30%	30.60%	31.10%	37.10%			
	Median (months, 95% CI)	24.7 (14.7–34.7)	18.6 (16.0–21.2)	28.1 (20.6–35.7)	32.6 (22.2–43.0)	0.223	0.22	0.047
Age at diagnosis (years)	Mean±SD	61.9±10.4	53.7±9.5	66.1±7.4	63.7±9.2	<0.001	<0.001	0.129
	≤49	22 (13.6%)	453 (34.3%)	3 (1.8%)	13 (9.6%)	<0.001	<0.001	0.367
	≥50	140 (86.4%)	867 (65.7%)	164 (98.2%)	122 (90.4%)			
Sex	Male	125 (77.2%)	1107 (83.9%)	132 (79.0%)	135 (100.0%)	0.035	0.691	<0.001
	Female	37 (22.8%)	213 (16.1%)	35 (21.0%)	0 (0.0%)			
ECOG performance status	0	71 (43.8%)	567 (43.0%)	76 (45.5%)	62 (45.9%)	0.861	0.698	0.453
	1	85 (52.5%)	713 (54.0%)	82 (49.1%)	70 (51.9%)			
	2	6 (3.7%)	40 (3.0%)	8 (4.8%)	2 (1.5%)			
	3	0%	0 (0%)	1 (0.6%)	1 (0.7%)			
Child–Pugh class	A	136 (84.0%)	1077 (81.6%)	142 (85.0%)	110 (81.5%)	0.441	0.79	0.473
	B	25 (15.4%)	217 (16.4%)	23 (13.8%)	22 (16.3%)			
	C	1 (0.6%)	26 (2.0%)	2 (1.2%)	3 (2.2%)			
BCLC stage	0	5 (3.1%)	67 (5.1%)	5 (3.0%)	7 (5.2%)	0.395	0.981	0.341
	A	32 (19.8%)	261 (19.8%)	34 (20.4%)	32 (23.7%)			
	B	19 (11.7%)	115 (8.7%)	21 (12.6%)	13 (9.6%)			
	C	105 (64.8%)	851 (64.5%)	105 (62.9%)	79 (58.5%)			
	D	1 (0.6%)	26 (2.0%)	2 (1.2%)	4 (3.0%)			

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 1. (continued)

Characteristics (n=1,784)		Cryptogenic (n=162) (9.1%)	Cause of HCC			cHCC		
			HBV (n=1,320) (74.0%)	HCV (n=167) (9.4%)	Alcohol (n=135) (7.5%)	vs. HBV p value	vs. HCV p value	vs. Alcohol p value
mUICC stage	I	11 (6.8%)	121 (9.2%)	12 (7.2%)	12 (8.9%)	0.05	0.371	0.188
	II	53 (32.7%)	374 (28.3%)	53 (31.7%)	51 (37.8%)			
	III	45 (27.8%)	297 (22.5%)	56 (33.5%)	38 (28.1%)			
	IVa	26 (16.0%)	338 (25.6%)	30 (18.0%)	24 (17.8%)			
	IVb	27 (16.7%)	190 (14.4%)	16 (9.6%)	10 (7.4%)			
MELD score	Mean	9.6±3.4	10.2±3.5	9.6±2.8	10.1±3.8	0.042	0.838	0.184
	<10	107 (66.1%)	819 (62.0%)	106 (63.5%)	83 (61.5%)	0.011	0.714	0.301
	≥10, <20	53 (32.7%)	467 (35.4%)	60 (35.9%)	48 (35.6%)			
	≥20, <30	1 (0.6%)	34 (2.6%)	1 (0.6%)	4 (3.0%)			
	≥30	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Tumor number	1	95 (58.6%)	677 (51.3%)	69 (41.3%)	81 (60.0%)	0.165	0.002	0.845
	2–3	28 (17.3%)	299 (22.6%)	53 (31.7%)	20 (14.8%)			
	≥4	39 (24.1%)	344 (26.1%)	45 (27.0%)	34 (25.2%)			
Tumor size (cm)	Mean	7.4±5.0	6.9±5.0	5.4±4.1	5.9±4.5	0.194	<0.001	0.007
	<2	12 (7.4%)	176 (13.3%)	27 (16.2%)	19 (14.1%)	0.111	0.001	0.03
	≥2, <5	59 (36.4%)	432 (32.7%)	73 (43.7%)	56 (41.5%)			
	≥5, <10	42 (25.9%)	373 (28.3%)	46 (27.5%)	37 (27.4%)			
	≥10	49 (30.2%)	339 (25.7%)	21 (12.6%)	23 (17.0%)			
Tumor type	Well defined	107 (66.0%)	855 (64.8%)	134 (80.2%)	100 (74.1%)	0.794	0.004	0.163
	Poorly defined	55 (34.0%)	465 (35.2%)	33 (19.8%)	35 (25.9%)			
Liver cirrhosis		21 (13.0%)	536 (40.6%)	52 (31.1%)	60 (44.4%)	<0.001	<0.001	<0.001
Mean platelet count (10^3/uL)		188.4±94.3	157.7±88.9	136.0±70.7	167.8±78.5	<0.001	<0.001	0.045
Mean APRI		1.3±1.6	1.9±3.1	2.0±1.9	1.0±0.8	0.023	<0.001	0.032

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 1. (continued)

Characteristics (n=1,784)		Cause of HCC				cHCC		
		Cryptogenic (n=162) (9.1%)	HBV (n=1,320) (74.0%)	HCV (n=167) (9.4%)	Alcohol (n=135) (7.5%)	vs. HBV p value	vs. HCV p value	vs. Alcohol p value
APRI>1.5 *		40 (24.7%)	500 (37.9%)	88 (52.7%)	29 (21.5%)	0.001	<0.001	0.582
Portal vein tumor thrombosis	None	113 (69.8%)	832 (63.0%)	126 (75.4%)	101 (74.8%)	0.139	0.23	0.382
	1st or 2nd branch	38 (23.5%)	340 (25.8%)	36 (21.6%)	23 (17.0%)			
	Main	11 (6.8%)	148 (11.2%)	5 (3.0%)	11 (8.1%)			
Extrahepatic spread		31 (19.1%)	256 (19.4%)	148 (11.4%)	16 (11.9%)	1	0.065	0.11
AFP (ng/mL)	Median (Q1-Q3)	52.4 (5.3–1880.9)	2887.9 (21.2–4930.3)	56.9 (13.5–642.3)	12.6 (5.3–240.8)	<0.001[†]	0.377[†]	0.066[†]
	<20	69 (42.6%)	315 (23.9%)	55 (32.9%)	76 (56.3%)	<0.001	0.002	0.054
	≥20, <200	32 (19.8%)	294 (22.3%)	62 (37.1%)	23 (17.0%)			
	≥200	61 (37.7%)	711 (53.9%)	50 (29.9%)	36 (26.7%)			
Initial treatment	Liver transplantation	1 (0.6%)	24 (1.8%)	1 (0.6%)	1 (0.7%)	0.008	<0.001	0.006
	RFA	1 (0.6%)	47 (3.6%)	6 (3.6%)	6 (4.4%)			
	Resection	51 (31.5%)	259 (19.6%)	19 (11.4%)	26 (19.3%)			
	cTACE	75 (46.3%)	741 (56.17%)	130 (77.8%)	88 (65.2%)			
	Radiation therapy	9 (5.6%)	66 (5.0%)	4 (2.4%)	5 (3.7%)			
	Systemic cytotoxic chemotherapy	10 (6.2%)	61 (4.6%)	2 (1.2%)	2 (1.5%)			
	Sorafenib	4 (2.5%)	21 (1.6%)	1 (0.6%)	2 (1.5%)			
	Conservative management	11 (6.8%)	101 (7.7%)	4 (2.4%)	5 (3.7%)			

p value<0.05, statistically significant. YSR=year survival rate; CI=confidence interval. * APRI >1.5, predictive of significant fibrosis [13, 29]. † non-parametric test (because of non-normal distribution).

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 2. Comparison of survival rates between cHCC and HCC from other causes (HR of death through multivariate analysis)

		p value	HR	95% CI	
Cause of HCC	Cryptogenic		1		
	HBV	0.0383	1.251	1.012	1.547
	HCV	0.9256	0.987	0.747	1.304
	Alcohol	0.9211	1.015	0.756	1.363

cHCC had the largest proportion of female patients (22.8%) compared with HBV HCC (16.1%, p=0.035), HCV HCC (21.0%, p=0.691), and alcoholic HCC (0%, p<0.001). The performance status, Child–Pugh class, and BCLC stage were not different among the groups of HCC patients. The mUICC stage of cHCC at diagnosis was lower than that of HBV HCC (p=0.050). A MELD score <10 was most frequent (66.1%) in cHCC, and the MELD score distribution of cHCC had a higher proportion of lower stages than that of HBV HCC (p=0.011).

cHCC patients had the second-highest proportion of single hepatic lesions (58.6%), after alcohol HCC (60.0%), and the number of cHCC nodules was smaller than that of HCV HCC (p=0.002). cHCC patients had the largest tumors (mean 7.4 cm; 30.2% >10 cm) among HCC patients, and the tumor size distribution showed a smaller proportion of tumors <2 cm than for HCV and alcoholic HCC (p<0.05). In addition, as determined by CT imaging, cHCC patients had the second-highest proportion of poorly defined tumors (34.0%), after HBV HCC (35.2%), and significantly more than that of HCV HCC (19.8%, p=0.004).

Initial diagnostic CT imaging studies revealed that cHCC patients had the lowest prevalence of cirrhosis (13.0%), followed by HCV HCC (31.1%), HBV HCC (40.6%), and alcoholic HCC (44.4%) patients. cHCC patients had the highest mean platelet count (188.4 ×10^3/ μL). cHCC patients also had lower mean APRI values (1.3) than patients with HBV HCC (1.9, p=0.023) and HCV HCC (2.0, p<0.001). The proportion of cryptogenic patients with APRI >1.5, which is a predictive of significant fibrosis [13, 35], was lower than that of HBV HCC patients (24.7% vs. 37.9%, p=0.001) and HCV HCC patients (24.7% vs. 52.7%, respectively, p<0.001).

cHCC patients had the second-highest frequency of portal vein tumor invasion and extrahepatic spread after HBV HCC (30.3% vs. 37.0% and 19.1% vs 19.4%, respectively, p>0.05).

cHCC had the second highest number of patients with normal α-fetoprotein (AFP) values (42.6%), after those of alcoholic HCC (56.3%). Median AFP levels were significantly different between cHCC and HBV HCC (52.4 vs. 287.9 ng/mL, p<0.001). Resection was performed at a higher proportion of all treatment modalities for cHCC (31.5%), compared with HBV HCC (19.6%), HCV HCC (11.4%), and alcoholic HCC (19.3%).

Comparisons of Clinical and Laboratory Variables

Clinical and laboratory variables, including BMI, serum glucose, and total cholesterol levels are shown in table 3. There was no significant difference in mean BMI among HCC patients according to cause. Nearly one-third (29.0%) of cHCC patients were overweight (BMI ≥25), but these rates were not significantly different from those with HCC from other causes. The proportion of cHCC patients who were obese (BMI ≥30) was the highest (3.7%) among HCC patients, but was not significantly different among the various patient groups. Hypertension was more prevalent in patients with cHCC than in patients with HBV HCC (49.4% vs. 39.9%, p=0.022) but not in patients with HCV HCC (53.9%) or alcoholic HCC (50.4%).

Hyperglycemia was more prevalent in patients with cHCC than in patients with HBV HCC (45.7% vs. 32.3%, p<0.001) but not in patients with HCV HCC (38.3%) or alcoholic HCC (51.1%). The mean total cholesterol levels were not significantly different among the HCC
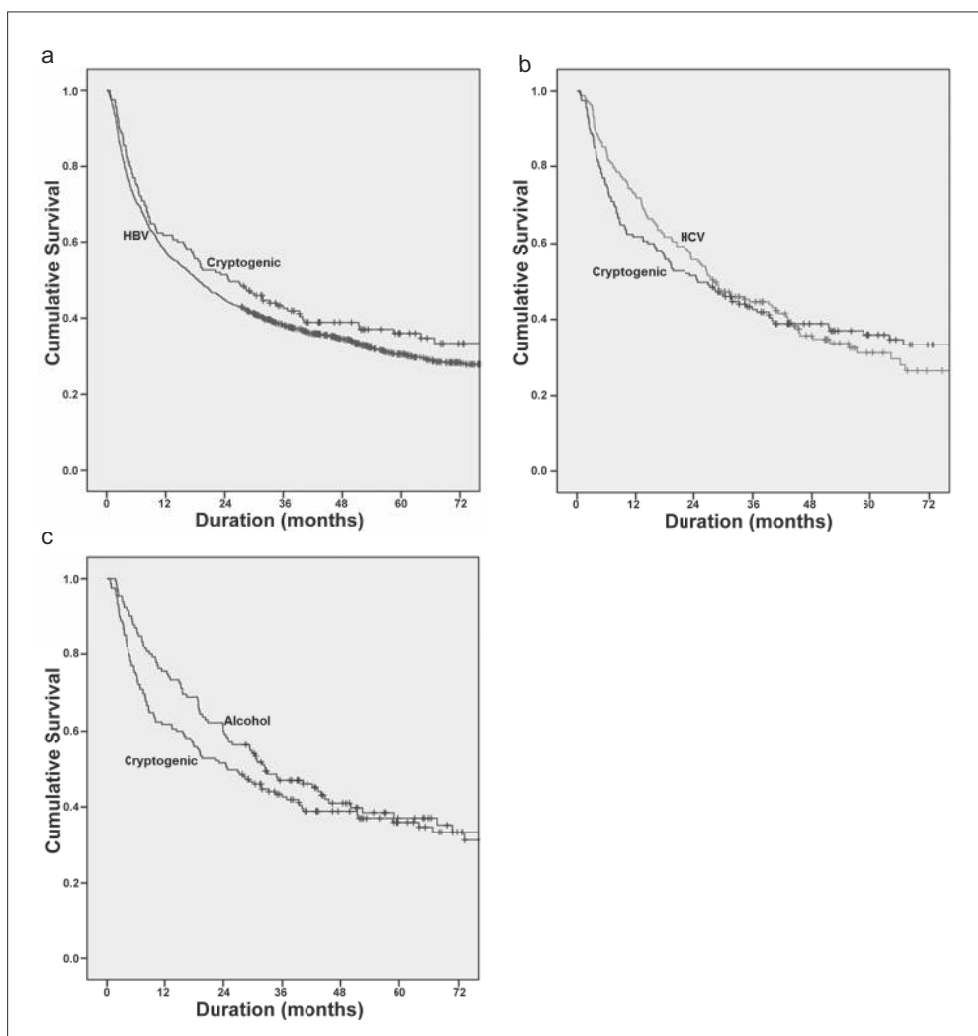
Fig. 1. Comparison of overall survival between cHCC and HBV HCC (**a**), HCV HCC (**b**), and alcoholic HCC (**c**). There were no significant differences between the groups in terms of survival rates (all p values >0.05).

groups; however, the incidence of hypercholesterolemia was higher in cHCC patients than in HCV HCC patients (4.9% vs. 0.6%, p=0.018).

Initial CT imaging studies revealed that fatty liver was more prevalent in patients with cHCC than in patients with HBV HCC (26.5% vs. 19.4%, p=0.038), but not for patients with HCV HCC (35.9%) or alcoholic HCC (40.7%).

The median AST value was significantly lower in patients with cHCC (48.0 IU/L) than in patients with HCC of viral-origin (HBV HCC, 59.0 IU/L and HCV HCC, 74.0 IU/L, both p<0.001). Normal AST/ALT values were more frequent in patients with cryptogenic and alcoholic HCC. The median ALT value was also significantly lower in patients with cHCC (30.5 IU/L) than in patients with viral-origin HCC (HBV HCC, 41.0 IU/L and HCV HCC, 44.0 IU/L, both p<0.001).

Comparisons According to the Presence of Anti-HBc Antibodies in cHCC Patients

Among cHCC patients, 137 (84.6%) had anti-HBc antibodies. The cHCC patients without anti-HBc antibodies had better Eastern Cooperative Oncology Group (ECOG) performance,

Table 3. Metabolic factors and laboratory characteristics of 1,784 HCC patients: comparison between cHCC and HCC from other causes

Cause of HCC (n=1,784)	Cryptogenic (n=162)	Cause of HCC			cHCC		
		HBV (n=1,320)	HCV (n=167)	Alcohol (n=135)	vs. HBV p value	vs. HCV p value	vs. Alcohol p value
Mean BMI (kg/m²)	23.5±3.2	23.1±3.2	23.6±3.1	23.6±3.3	0.231	0.581	0.694
Underweight (<18.5)	5 (3.1%)	86 (6.5%)	4 (2.4%)	6 (4.4%)	0.168	0.546	0.354
Normal weight (18.5–24.9)	110 (67.9%)	881 (66.7%)	109 (65.3%)	80 (59.3%)			
Overweight (25–29.9)	41 (25.3%)	327 (24.8%)	51 (30.5%)	45 (33.3%)			
Obese (≥30)	6 (3.7%)	26 (2.0%)	3 (1.8%)	4 (3.0%)			
Hypertension	80 (49.4%)	527 (39.9%)	90 (53.9%)	68 (50.4%)	0.022	0.441	0.907
Hyperglycemia	74 (45.7%)	426 (32.3%)	64 (38.3%)	69 (51.1%)	<0.001	0.182	0.354
Mean total cholesterol (mg/dL)	155.8±48.7	161.9±50.7	148.2±35.3	148.5±39.1	0.147	0.108	0.159
Hypercholesterolemia (total cholesterol >240 mg/dL)	8 (4.9%)	79 (6.0%)	1 (0.6%)	3 (2.2%)	0.724	0.018	0.356
Fatty liver	43 (26.5%)	256 (19.4%)	60 (35.9%)	55 (40.7%)	0.038	0.075	0.013
Median AST (IU/L) (Q1-Q3)	48.0 (30.0–84.3)	59.0 (39.0–98.0)	74.0 (48.0–102.0)	42.0 (32.0–61.0)	<0.001†	<0.001†	0.157†
AST>40 (upper normal limit)	91 (56.2%)	1002 (75.9%)	138 (82.6%)	73 (54.1%)	<0.001	<0.001	0.727
Median ALT (IU/L) (Q1-Q3)	30.5 (18.0–54.0)	41.0 (27.0–65.0)	44.0 (27.0–73.0)	29.0 (19.0–40.0)	<0.001†	<0.001†	0.217†
ALT>40 (upper normal limit)	59 (36.4%)	701 (53.1%)	94 (56.3%)	37 (27.4%)	<0.001	<0.001	0.107

p-value <0.05, statistically significant. † Non-parametric test (because of non-normal distribution).

30

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Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

lower AFP levels compared to the group with anti-HBc antibodies (table 4). Interestingly, cHCC patients with anti-HBc antibodies were older, showed lower the MELD scores, AFP levels, lower AST/ALT levels, and a smaller proportion of patients with cirrhosis than patients with HBV HCC.

Discussion

cHCC comprised 9.1% of HCC cases in this study. The reported incidence of cHCC, including NBNCNA HCC, in South Korea has increased from 2.3% in 1993–1995 to 5.4% in 2000–2002 ([22], and from 3.8% in 2001–2005 to 12.2% in 2006–2010 [23]. In another study covering 2003–2012, cHCC comprised 6.8% of HCC cases [21]. The proportion of cHCC patients among all HCC patients is believed to be rising because of the increasing prevalence of NAFLD and the metabolic syndrome [12, 36].

In this study, cHCC patients had a poor median survival time (24.7 months). This fact could not be attributed to poor liver function, but could be attributable to tumor characteristics, i.e., large tumor size (mean size 7.4 cm), poorly defined tumor type (34.0%), portal vein invasion (30.4%), and extrahepatic spread (19.1%). Poor median survival could have resulted also from delay in making the diagnosis, as reflected in the lowest rate (6.8%) of mUICC stage I tumors among the four kinds of HCC studied. Perhaps patients with NAFLD, the putative major cause of cHCC, had fewer symptoms than patients with chronic HBV/HCV hepatitis or alcoholic liver diseases, and therefore less frequently received liver screening [37]. Thus, the diagnosis of cHCC might be delayed, meaning that the tumors are larger and more aggressive than other HCCs when discovered. Nonetheless, cHCC patients had better survival than HBV HCC patients (HR 1:1.251) according to multivariate analysis. Consequently, patients with NAFLD should undergo regular surveillance for the development of HCC. In addition, the proportion of cHCC patients with AFP values >200 ng/mL was the second highest, which might result from the larger size and more aggressive clinical characteristics of cHCC at diagnosis.

cHCC patients in the current study had the lowest prevalence of cirrhosis in initial imaging studies, and all HCC patients showed a tendency toward a lower prevalence of cirrhosis regardless of cause compared to that found in other studies [38]. These results might be caused by ambiguity of the clinical definition of cirrhosis and limitations in the radiological diagnosis of cirrhosis, including bias in individual radiologist's readings. To compensate for these weaknesses, we adopted the APRI score for analyzing the severity of liver fibrosis. According to the APRI scores, cHCC patients had less liver fibrosis than patients with viral-induced HCC, but more than patients with alcoholic HCC. The high mean platelet count of cHCC patients also may reflect lower levels of liver fibrosis.

In this study, the proportion of female patients was highest (22.8%) in the cHCC group, and was significantly higher than that in HBV HCC patients (16.1%). This might be related to the higher prevalence of NAFLD in older women [39]. However, the relationship between gender and the etiology of HCC needs further evaluation.

The proportion of obese (BMI ≥30) patients was higher for cHCC than for the other types of HCC, but the difference was not statistically significant. The incidence of metabolic syndrome was similar for cryptogenic, HCV, and alcoholic HCC. HCV and alcoholic HCC are often accompanied by the metabolic syndrome, which can obscure the causal differences between the various kinds of HCC [40]. In our study, the proportion of overweight (BMI ≥25) patients with cHCC was lower than that in other reports [21, 24]. This discrepancy may be attributable to differences in the proportion of patients with advanced HCC and overlapping

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 4. Survival, clinicopathologic, and metabolic characteristics of patients with cHCC (with and without anti-HBc IgG antibodies) and with HBV HCC

HCC		cHCC Anti-HBc IgG (−) (n=25) (15.4%)	cHCC Anti-HBc IgG (+) (n=137) (84.6%)	HBV HCC HBs Ag (+) (n=1,320)	vs. Anti-HBc IgG (−) p value	Anti-HBc IgG (+) vs. HBs Ag (+) p value
Survival	1 YSR	56.0%	62.8%	57.5%	0.734	0.220
	3 YSR	40.0%	42.6%	38.3%		
	5 YSR	40.0%	34.8%	30.6%		
	Median(months, 95% CI)	17.8 (1.3–34.3)	27.0 (16.5–37.5)	18.6 (16.0–21.2)	0.462	0.169
Age at diagnosis (years)	Mean	65.0±11.3	61.4±10.2	53.7±9.5	0.112	<0.001
	≤49	2 (8.0%)	20 (14.6%)	453 (34.3%)	0.532	<0.001
	≥50	23 (92.0%)	117 (85.4%)	867 (65.7%)		
Sex	Male	20 (80.0%)	105 (76.6%)	1107 (83.9%)	0.802	0.396
	Female	5 (20.0%)	32 (23.4%)	213 (16.1%)		
ECOG performance status	0	16 (64.0%)	55 (40.1%)	567 (43.0%)	0.022	0.807
	1	7 (28.0%)	78 (56.9%)	713 (54.0%)		
	2	2 (8.0%)	4 (2.9%)	40 (3.0%)		
	3	0%	0%	0 (0%)		
Child–Pugh class	A	21 (84.0%)	115 (83.9%)	1077 (81.6%)	0.910	0.547
	B	4 (16.0%)	21 (15.3%)	217 (16.4%)		
	C	0 (0%)	1 (0.7%)	26 (2.0%)		
BCLC stage	0	1 (4.0%)	4 (2.9%)	67 (5.1%)	0.516	0.421
	A	8 (32.0%)	24 (17.5%)	261 (19.8%)		
	B	3 (12.0%)	16 (11.7%)	115 (8.7%)		
	C	13 (52.0%)	92 (67.2%)	851 (64.5%)		
	D	0 (0%)	1 (0.7%)	26 (2.0%)		

KARGER

Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

Table 4. (continued)

HCC		cHCC Anti-HBc IgG (−) (n=25) (15.4%)	cHCC Anti-HBc IgG (+) (n=137) (84.6%)	HBV HCC HBs Ag (+) (n=1,320)	Anti-HBc IgG (−) vs. Anti-HBc IgG (−) p value	Anti-HBc IgG (+) vs. HBs Ag (+) p value
mUICC stage	I	2 (8.0%)	9 (6.6%)	121 (9.2%)	0.725	0.094
	II	9 (36.0%)	44 (32.1%)	374 (28.3%)		
	III	5 (20.0%)	40 (29.2%)	297 (22.5%)		
	IVa	3 (12.0%)	23 (16.8%)	338 (25.6%)		
	IVb	6 (24.0%)	21 (15.3%) 15.2%	190 (14.4%)		
MELD score	Mean	8.9±1.7	9.7±3.6	10.2±3.5	0.114	0.128
	<10	18 (72.0%)	89 (64.9%)	819 (62.0%)	0.867	0.009
	≥10, <20	7 (28.0%)	46 (33.6%)	467 (35.4%)		
	≥20, <30	0 (0%)	1 (0.7%)	34 (2.6%)		
	≥30	0 (0%)	1 (0.7%)	0 (0.0%)		
Tumor number	1	16 (64.0%)	79 (57.7%)	677 (51.3%)	0.828	0.283
	2–3	4 (16.0%)	24 (17.5%)	299 (22.6%)		
	≥4	5 (20.0%)	34 (24.8%)	344 (26.1%)		
Tumor size (cm)	Mean	7.4±4.7	7.4±5.1	6.9±5.0	0.963	0.222
	<2	2 (8.0%)	10 (7.3%)	176 (13.3%)	0.969	0.140
	≥2, <5	8 (32.0%)	51 (37.2%)	432 (32.7%)		
	≥5, <10	7 (28.0%)	35 (25.5%)	373 (28.3%)		
	≥10	8 (32.0%)	41 (29.9%)	339 (25.7%)		
Tumor type	Well defined	17 (68.0%)	90 (65.7%)	855 (64.8%)	1.000	0.852
	Poorly defined	8 (32.0%)	47 (34.3%)	465 (35.2%)		

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Table 4. (continued)

HCC		cHCC Anti-HBc IgG (−) (n=25) (15.4%)	cHCC Anti-HBc IgG (+) (n=137) (84.6%)	HBV HCC HBs Ag (+) (n=1,320)	vs. Anti-HBc IgG (−) p value	Anti-HBc IgG (+) vs. HBs Ag (+) p value
Liver cirrhosis		3 (12.0%)	18 (13.1%)	536 (40.6%)	1.000	0.002
Mean platelet count (10^3/uL)		189.9±95.3	188.1±94.5	157.7±88.9	0.929	<0.001
Mean APRI		1.7±1.9	1.2±1.5	1.9±3.1	0.217	0.019
APRI>1.5 *		9 (36.0%)	31 (22.6%)	500 (37.9%)	0.205	<0.001
Portal vein tumor thrombosis	None	18 (72.0%)	95 (69.3%)	832 (63.0%)	0.386	0.125
	1st or 2nd branch	4 (16.0%)	34 (24.8%)	340 (25.8%)		
	Main	3 (12.0%)	8 (5.8%)	148 (11.2%)		
Extrahepatic spread		6 (24.0%)	25 (18.2%)	256 (19.4%)	0.580	0.820
AFP (ng/mL)	Median (Q1-Q3)	5.6 (3.3–2084.6)	72.2 (7.5–1767.6)	287.9 (21.2–4930.3)	0.034†	<0.001†
	<20	16 9 (64.0%)	53 (38.7%)	315 (23.9%)	0.028	<0.001
	≥20, <200	1 (4.0%)	31 (22.6%)	294 (22.3%)		
	≥200	8 (32.0%)	53 (38.7%)	711 (53.9%)		
Mean BMI (kg/m²)		22.8±2.5	23.6±3.3	23.1±3.2	0.150	0.100
Hypertension		15 (60.0%)	65 (47.4%)	527 (39.9%)	0.282	0.100
Hyperglycemia		11 (44.0%)	63 (46.0%)	426 (32.3%)	1.000	0.002
Hypercholesterolemia		2 (8.0%)	6 (4.4%)	79 (6.0%)	0.357	0.567
Fatty liver		9 (36.0%)	34 (24.8%)	256 (19.4%)	0.324	0.144
AST>40 (upper normal limit)		15 (60.0%)	76 (55.5%)	1002 (75.9%)	0.827	<0.001
Median AST (IU/L) (Q1-Q3)		53.0 (31.5–120.0)	48.0 (29.5–83.5)	59.0 (39.0–98.0)	0.437	<0.001
ALT>40 (upper normal limit)		9 (36.0%)	50 (36.5%)	701 (53.1%)	1.000	<0.001
Median ALT (IU/L) (Q1-Q3)		32.0 (16.5–70.5)	30.0 (19.5–53.0)	41.0 (27.0–65.0)	0.946†	<0.001†

* APRI >1.5, predictive of significant fibrosis [13, 29]. † Non-parametric test (because of non-normal distribution).

34

Liver Cancer

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Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

occurrence of metabolic syndrome in the study population. Unfortunately, the inherent limitations of our study (because of its retrospective nature) meant that we did not have information regarding the history of obesity and changes in weight after the development of HCC.

In comparison to other reports [18, 41, 42], our patients had a lower prevalence of diabetes, which may be related to the low prevalence of cirrhosis in our study. A Japanese study also reported that underlying cirrhosis affects the prevalence of diabetes in patients with NAFLD or HCV [43].

The proportion of cHCC patients with hypertension and fatty liver cHCC was higher than that for HBV HCC, but not for HCV HCC or alcoholic HCC. One possible reason is that patients with HCV or alcoholic HCC are likely to have concurrent metabolic syndrome, as mentioned above. In other reports also, the proportion of cHCC patients with hypertension was higher than that of HBV HCC patients [21, 24]. Depending on the definition of hypertension, the proportion of hypertensive patients will change; nonetheless, we could determine the relative proportions of patients with hypertension for HCC with different causes.

The fact that HBV is endemic in Korea could be the reason for the presence of anti-HBc antibodies in so many patients with cHCC. It was considered that the presence of anti-HBc antibodies might modify the characteristics of HCC toward those of HBV HCC. However, analysis of data for cHCC patients with and without anti-HBc antibodies showed significant differences between HBV HCC and cHCC with anti-HBc antibodies. According to the protocol of this study, if non-HCV, non-alcoholic patients did not have HBsAg, regardless the presence of anti-HBc antibodies, they were classified as having cHCC. However, many patients with cHCC had anti-HBc antibodies, and these patients showed some tumor characteristics intermediate between those of HBV HCC patients and those of "pure" cHCC patients.

This cohort study had several limitations. First, cHCC in South Korea includes HCC from causes other than NAFLD, such as a past HBV infection and unknown causes. The possible role of past HBV infections is uncertain in cHCC patients with anti-HBc antibodies. Second, patient histories of alcohol consumption were obtained through self-reporting, which may not be reliable. It is possible that the proportion of patients who had alcoholic liver disease as the cause of HCC was underestimated [25], and this underestimation could have affected the observed clinical features of the population classified as cHCC. Third, metabolic factors resulting from the metabolic syndrome were not clearly implicated as the main cause of cHCC in this study. Values of BMI, hypertension, and hyperglycemia obtained only from the initial questionnaire and initial laboratory studies could contain false negatives or positives. Finally, the diagnosis of cirrhosis or fatty liver was made based on the initial CT imaging studies only. However, bias from individual radiologists may have skewed and underestimated the results.

In summary, cHCC comprised 9.1% of HCC patients. The median survival times of cHCC was the second poorest after HBV HCC. cHCC patients had the largest tumors and the second highest proportion of poor prognostic factors such as the proportion of poorly defined tumors and extrahepatic spread in imaging studies, but had the lowest prevalence of cirrhosis on initial imaging studies. cHCC patients were shown by multivariate analysis to have better survival than HBV HCC patients. This study did not find conclusive evidence of the effects of clinical and laboratory variables such as BMI, glucose, and cholesterol levels in our population, likely because HCV HCC and alcoholic HCC could be affected by comorbid metabolic syndrome. cHCC patients had lower AST/ALT levels than those with viral-induced HCC. Most patients with cHCC had anti-HBc antibodies, but we could not determine whether the presence of anti-HBc antibodies affected clinical characteristics. It is hoped that this study will contribute to understanding of the behavior and appropriate management of cHCC in HBV-endemic areas such as South Korea.

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35

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Kwak et al.: Characteristics of Cryptogenic HCC in an HBV-Endemic Area

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Disclosures

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