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Incidence and Clinical Features of Hepatitis C Virus-associated Hepatocellular Carcinoma Patients without Liver Cirrhosis in Hepatitis B Virus-endemic Area

Jongbeom Shin*, Jung Hwan Yu*, Young-Joo Jin, Jin-Woo Lee

Division of Gastroenterology, Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, Korea

Background/objective: Hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) is rarely observed in patients without liver cirrhosis (LC). We evaluated the incidence and clinical feature of HCV-associated HCC patients with or without LC.

Methods: The medical records of 1,516 patients diagnosed as having primary HCC at our hospital between January 2005 and December 2017 were retrospectively reviewed. Of these, 154 (10.2%) HCV-associated HCC patients were analyzed. LC was diagnosed histologically or clinically.

Results: Seventeen (11.0%) of the 154 patients had non-cirrhotic HCC, and all were of Child-Turcotte-Pugh (CTP) class A, Among the 17 patients, 88.2% were male, all had nodular type HCC, and only 2 (11.8%) were under HCC surveillance. Median overall survival (OS) of HCV-associated HCC patients with and without LC was 15 months and 37 months, respectively. Cumulative OS rates were not different between non-cirrhotic patients and cirrhotic patients with CTP class A (P=0.229). Cumulative OS rates were significantly higher in non-cirrhotic patients than in cirrhotic patients of CTP class B (P<0.001) or C (P<0.001). Multivariate analyses showed serum AST (hazard ratio [HR] 1.01, P=0.003) and AFP levels (HR 1.01, P=0.016), antiviral therapy (HR 0.25, P=0.022), and LC of CTP class B (HR, 5.24, P=0.006) or C (HR 21.79, P<0.001) were significantly associated with prognosis in HCV-associated HCC patients.

Conclusions: HCC in a non-cirrhotic liver was found in 11% of HCV-associated HCC patients. OSs of HCV-associated HCC patients were better in those of CTP A, regardless of LC than in those with LC of CTP class B or C. **(J Liver Cancer 2021;21:34-44)**

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common human cancer and the fourth in terms of cancer-related global mortality.[1] Underlying liver cirrhosis (LC) is the main risk factor for HCC development regardless of underlying liver disease.[2] However, not all HCC patients have LC, and

Corresponding author : Young-Joo Jin

Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, 27 Inhang-ro, Jung-gu, Incheon 22332, Korea
Tel. +82-32-890-2548, Fax. +82-32-890-2549
E-mail; jyj412@hanmail.net
https://orcid.org/0000-0002-7449-2461
* These two authors are co-first authors who equally contributed to this work.

HCCs have been reported to develop occasionally in non-cirrhotic livers.[3-5] Among Asian hepatitis B virus (HBV) carriers without LC, HCC risk remains high regardless of HBV replication status.[6-8] On the other hand, HCC development in hepatitis C virus (HCV) patients without LC has not been clearly defined, although the risk of HCC in chronic HCV patients with LC has been well established.[9,10]

In HCV patients with LC, the annual incidence of HCC is known to range between 2% and 8%,[10,11] but the risk of HCC development in HCV patients without LC has been reported to be much lower.[12,13] In a previous study, the 5-year risk of HCC development in HCV patients without LC was reported to be 4.8%.[12] Recently, more HCV patients than ever have received oral direct acting antiviral (DAA) therapy for chronic HCV infection. And, the risks of persistent chronic inflammation and progression to cirrhosis in these patients is expected to reduced.[14,15] Nonetheless, the occurrence of HCC was not reduced in HCV patients with LC treated with DAA.[16] Moreover, recent studies have reported HCC risk does not fully disappear in HCV patients without LC even after the achievement of sustained virologic response (SVR) on antiviral therapy (AVT) for chronic HCV infection.[17-19] However, these studies were conducted in Western countries, where HCV is the main etiology of HCC.[17-19] Although two recent studies analyzed the risks of HCC in HCV patients on AVT in HBV endemic areas,[20,21] these studies were conducted only on patients being treated on AVT for HCV and did not assess the clinical features of HCC in HCV patients without LC. Moreover, the proportion of HCV-associated HCC patients without underlying LC among all HCC patients has not been well defined in HBV-endemic areas, and the clinical features of these patients remain to be determined.

In this cross-sectional and longitudinal study, therefore, we retrospectively compared the incidences and clinical features of HCV-associated HCC patients with or without LC residing in an HBV-endemic area. In addition, we also evaluated the overall survivals (OSs) of these patients according to the Child-Turcotte Pugh (CTP) classification.

METHODS

1. Study subjects

Between January 2005 and December 2017, 1,552 patients were initially diagnosed with HCC at our hospital. Patients with a treatment history of HCC at other institutions before visiting our hospital were not enrolled. HCC was diagnosed based on the American Association for the Study of Liver Diseases (AASLD) guidelines.[22] Of these 1,552 patients, 36 patients with another combined malignancy or mixed type of HCC with cholangiocarcinoma were excluded (Fig. 1). Of the 1,516 HCC patients without another combined malignancy, 1,362 patients with HBV (n=985), alcohol-related HCC (n=217), non-alcoholic fatty liver disease (n=57), primary biliary cirrhosis (n=2), or cryptogenic disease (n=101) were also excluded (Fig. 1). The 154 (154/1,516, 10.2%) remaining HCV-related HCC patients were retrospectively enrolled in this study. All had been anti-HCV antibody positive for at least 6 months at enrollment. LC was diagnosed based on histologic findings, or clinically according to the presence of portal hypertension (HTN) (encephalopathy, esophageal varices, ascites, or splenomegaly, or a low (<100,000/mm^3) platelet count),[23] or radiologically according to ultrasonographic, computed tomographic, or magnetic resonance imaging (MRI) findings,[24,25] or based on aspartate aminotransferase (AST) to platelet ratio index (APRI) or fibrosis index based on four factors (FIB-4).[26,27]

At diagnosis of HCV-associated HCC, HCC patients were divided into two groups, that is, into HCCs that developed in a non-cirrhotic (non-cirrhotic group) and cirrhotic liver background (cirrhotic group), and their cross-sectional data were obtained. These patients were regularly followed up every 3 to 6 months by serum alpha-fetoprotein (AFP) measurement and ultrasonography (USG) or computed tomography,[28] and their longitudinal data were collected. Diabetes mellitus (DM) (type 2) was defined as a previous diagnosis or the taking of relevant medications at enrollment, and HTN was defined as a systolic blood pressure of ≥130 mmHg or taking relevant drugs at enrollment.[29] This study was approved by the Institutional Review Board of Inha University

Hospital, Incheon, South Korea (INHAUH 2017-11-017-002).

2. Statistical Analyses

Clinical variables of study subjects are presented as medians (ranges) for continuous variables, and as numbers (percentages) for categorical variables. The chi-square test, Fisher's exact test, or the Student's *t*-test were used to determine the significances of difference between categorical or continuous variables. Kaplan-Meier analysis and the log-rank test were used to analysis survival outcomes. In multivariate analyses, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated by Cox proportional hazards regression analysis to identify predictors of OS. These predictors were evaluated at time of initial HCC diagnosis, and clinical factors, such as, age, gender, body mass index (BMI), presence of DM or HTN, AST, alanine aminotransferase (ALT), CTP class, tumor number, size, and type, AFP, and Barcelona Clinical Liver Cancer (BCLC) stages were included in the analysis. SPSS ver. 19.0 (IBM Corp., Armonk, NY, USA) was used throughout, and two-tailed *P*-values of <0.05 were considered statistically significant.

RESULTS

1. Baseline characteristics of the study subjects

Baseline clinical characteristics of the 154 study subjects are shown in Table 1. Of the 1,516 primary HCC patients without other combined malignancies, 154 (10.2%) patients were diagnosed as having HCV-associated HCC (Fig. 1). Of these 154 patients, 17 (11.0%) were the non-cirrhotic group, and 137 (89.0%) were the cirrhotic group (Table 1). Median age of the 154 study subjects was 66 years (range, 41-87 years), and 99 (64.3%) were male. Median BMI was 24.2 kg/m^2 (range, 13.8-43.3 kg/m^2), and DM and HTN were present in 58 (37.7%) and 66 (42.9%), respectively. One hundred three (66.9%) of the study subjects were of CTP class A, and 22 (14.3%) had experience of antiviral treatment (AVT). Al-

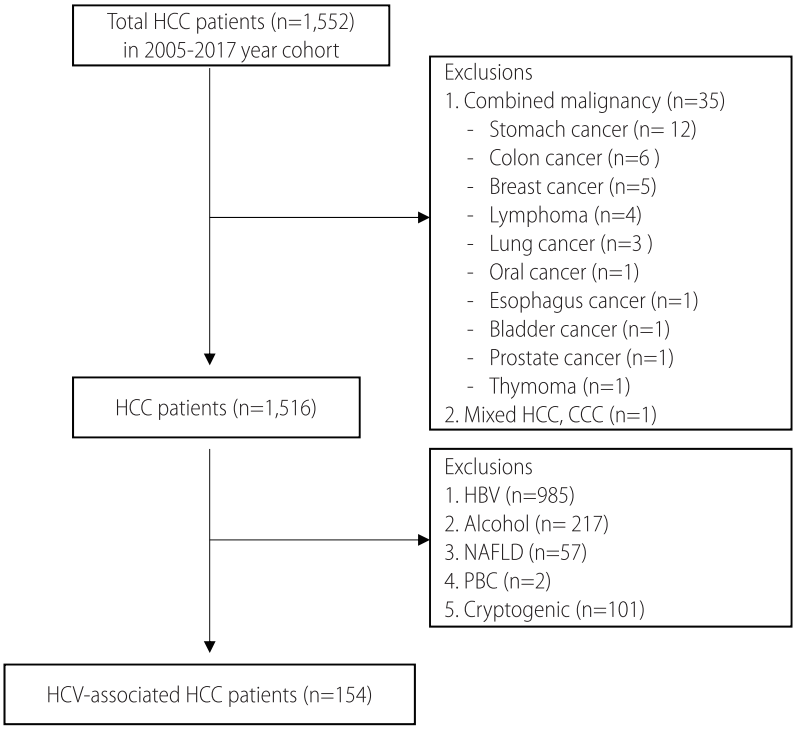

Figure 1. Study population. One hundred and fifty-four hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) patients were enrolled in this study. CCC, cholangiocarcinoma; HBV, hepatitis B virus; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis.

Table 1. Baseline clinical characteristics of patients

Variable	Total (n=154)	Cirrhotic (n=137, 89.0%)	Non-cirrhotic (n=17, 11.0%)	*P*-value*
Age (years)	66 (41-87)	66 (41-87)	68 (46-85)	0.463
Sex (male)	99 (64.3)	84 (61.3)	15 (88.2)	0.032†
BMI (kg/m^2)	24.2 (13.8-43.3)	24.3 (13.8-43.3)	23.2 (15.4-27.0)	0.027
DM	58 (37.7)	50 (36.5)	8 (47.1)	0.397
HTN	66 (42.9)	56 (40.9)	10 (58.8)	0.158
AST (IU/L)	63 (13-496)	68 (18-496)	41 (13-78)	<0.001
ALT (IU/L)	35 (8-222)	35 (8-222)	31 (12-71)	0.012
PLT (×10^3/uL)	110 (28-398)	106 (28-357)	209 (106-398)	<0.001
Albumin (mg/dL)	3.5 (1.5-4.6)	3.4 (1.5-4.5)	3.8 (3.2-4.6)	<0.001
T-bil. (mg/dL)	1.0 (0.2-16.0)	1.0 (0.2-16.0)	0.6 (0.4-2.1)	<0.001
PT (INR)	1.2 (0.9-3.8)	1.2 (0.9-3.8)	1.1 (0.9-1.5)	0.001
CTP (A/B/C)	103/41/10 (66.9/26.6/6.5)	86/41/10 (62.8/29.9/7.3)	17/0/0 (100/0/0)	0.004†
APRI	1.41 (0.11-15.91)	1.68 (0.27-15.91)	0.46 (0.11-0.91)	0.002
FIB-4	6.15 (0.70-44.92)	7.33 (1.14-44.92)	1.96 (0.7-6.56)	0.001
AVT (yes)	22 (14.3)	20 (14.6)	2 (11.8)	1.000†
Drugs (IFN/DAA)	20/2 (1.3/85.7)	18/2 (90.0/10.0)	2/0 (100/0)	1.000†
SVR (+, yes/no)	4/18 (18.2/81.8)	4/16 (20/80)	0/2 (0/100)	1.000†
AFP (ng/mL)	36.4 (1.3-6.1×10^4)	41.5 (1.3-6.1×10^4)	9.2 (2.9-1.9×10^3)	0.001
Tm. characteristics				
Type (nodular/diffuse)	149/5 (96.8/3.2)	132/5 (96.4/3.6)	17/0 (100/0)	1.000†
Number (1/≥2)	86/68 (55.8/44.2)	76/61 (55.5/44.5)	10/7 (58.8/41.2)	0.793
Size (cm)	2.7 (1.0-16.0)	2.6 (1.0-16.0)	4.2 (2.1-8.3)	0.09
PVT (presence)	24 (15.6)	23 (16.8)	1 (5.9)	0.475†
Metastasis (presence)	5 (3.2)	5 (3.6)	0	1.000†
BCLC stage				
0-A/B-D	94/60 (61/39)	82/55 (59.9/40.1)	12/5 (70.6/29.4)	0.392
Initial treatment				
Curative-intent‡	30 (19.5)	25 (18.2)	5 (29.4)	0.273
Initial treatment type				0.025†
OP	12 (7.8)	8 (5.8)	4 (23,5)	
RFA	18 (11.7)	17 (12.4)	1 (5.9)	
TACE	86 (55.8)	75 (54.7)	11 (64.7)	
Supportive care	29 (18.8)	29 (21.2)	0	
Transfer	9 (5.8)	8 (5.8)	1 (5.9)	
FU duration (months)	18 (1-142)	15 (1-142)	37.0 (4-100)	0.019

Values are presented as median (range) or number (%) unless otherwise indicated.
BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet; T-bil, total bilirubin; PT, prothrombin time; INR, international normalized ratio; CTP, Child-Turcotte-Pugh classification; APRI, aminotransferase to platelet ratio index; FIB-4, fibrosis index based on four factors; AVT, antiviral therapy; IFN, interferon; DAA, direct acting antiviral; SVR, sustained virologic response; AFP, alpha-fetoprotein; Tm, tumor; PVT, portal vein thrombosis; BCLC, Barcelona clinic liver cancer; OP, operation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; FU, follow-up.
P values were calculated using the t-test, chi-square test, or †Fisher-exact test; ‡Curative-intent treatment: operation or radiofrequency ablation.

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Table 2. Clinical features of HCV-associated HCC cases without LC

Case No	Age (years)	Sex	BMI (kg/m^2)	AST (IU/L)	ALT (IU/L)	PLT (×10^3/uL)	AVT	AFP (ng/mL)	Under surveillance	Initial sx.	Tumor number	Tumor size (cm)	PVT presence	Within Milan	BCLC stage	Modified UICC stage	Initial Tx
1	75	M	25.6	34	41	209	Yes	87.5	No	No	1	5.0	No	Yes	A	II	OP
2	46	M	19.3	50	71	138	No	25.7	No	No	1	4.2	No	Yes	A	II	OP
3	67	M	25.3	46	67	283	No	761.0	No	RUQ pain	1	5.8	No	No	A	II	OP
4	85	M	15.4	51	57	302	No	4.0	No	No	2	6.2	Yes	No	C	IVA	TACE
5	59	M	24.9	42	39	205	Yes	2.9	Yes, USG q 1 year	No	2	5.6	No	No	B	III	TACE
6	54	M	22.4	67	31	398	No	256.0	No	Palpable mass	2	7.8	No	No	B	III	TACE
7	73	M	22.3	31	16	212	No	3.6	No	No	2	6.7	No	No	B	III	TACE
8	68	M	23.1	41	17	360	No	1,909.0	No	RUQ pain	2	2.4	No	Yes	B	III	TACE
9	60	M	25.2	27	13	151	No	3.8	No	Dyspnea	1	6.2	No	No	A	II	TACE
10	70	F	22.8	50	54	150	No	221.0	No	No	2	2.5	No	Yes	A	III	TACE
11	51	M	27.0	72	56	252	No	16.0	No	Abnormal LFT	2	2.2	No	Yes	A	II	TACE
12	74	M	24.8	26	35	106	No	7.0	No	No	1	2.7	No	Yes	A	II	TACE
13	60	M	19.3	13	15	285	No	4.8	No	No	1	4.0	No	Yes	A	II	TACE
14	70	F	24.5	31	18	133	No	3.4	No	No	1	3.1	No	Yes	A	II	RFA
15	82	M	23.2	31	18	168	No	8.8	No	RUQ pain	1	8.3	No	No	A	II	OP
16	67	M	20.0	41	12	135	No	13.1	Yes, USG q 1 year	No	1	2.4	No	Yes	A	II	Transfer
17	75	M	23.4	78	17	215	No	9.2	No	No	1	2.1	No	Yes	A	II	TACE

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LC, liver cirrhosis; BMI, body mass index; AST, alanine aspartate; ALT, alanine aminotransferase; PLT, platelet; AVT, antiviral therapy; AFP, alpha-fetoprotein; Sx, symptom; PVT, portal vein thrombosis; BCLC, Barcelona Clinical Liver Cancer; UICC, Union for International Cancer Control; Tx, treatment; M, male; OP, operation; RUQ, right upper quadrant; USG, ultrasonography; F, female; LFT, liver function test; RFA, radiofrequency ablation.

most all (n=149, 96.8%) patients had nodular type HCC, and 86 (55.8%) had a single HCC. Median tumor size was 2.7 cm (range, 1.0-16.0 cm), and 94 (61.0%) patients had HCC of BCLC stage 0 or A. Thirty (19.5%) patients underwent treatment with curative-intent, that is, surgical resection (n=12) or radiofrequency ablation (n=18). Overall median follow-up duration was 18.0 months (range, 1-142 months). Between the cirrhotic and non-cirrhotic groups, the proportion of males (P=0.032) or CTP class A (P=0.004), median platelet count (P<0.001), and median albumin level (P<0.001) were significantly higher in the non-cirrhotic group. Median follow-up duration was longer in the non-cirrhotic group (P=0.019), but median BMI, AST, ALT, total bilirubin, prothrombin time (PT), and AFP levels were significantly lower in the non-cirrhotic group (all P-values<0.05). A history of AVT for HCV infection before diagnosis of HCV-associated HCC and tumor characteristics were not significantly different in the two study groups (all P-values>0.05).

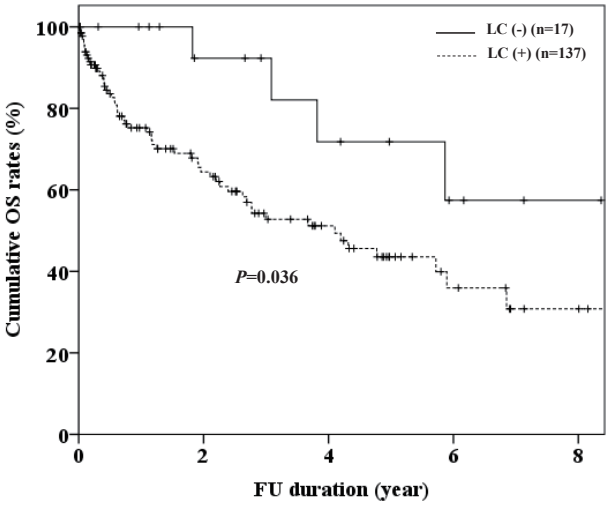

Figure 2. Relations between cumulative overall survival and the presence of liver cirrhosis. Cumulative overall survivals of hepatitis C virus-associated hepatocellular carcinoma patients without liver cirrhosis (LC) were significantly better than those of patients with LC (P=0.036). OS, overall survival; FU, follow-up.

2. Clinical features of HCV-associated HCC without LC

In order to identify the clinical features of patients in the non-cirrhotic group, 17 HCV-associated HCC cases without LC were individually assessed (Table 2). Median age in this group was 68 years (range 46-85 years), and 15 were male. Platelet counts were over 100 ($\times 10^3$/uL) in all patietns. Only two (11.8%) of the 17 patients had a history of AVT for HCV infection, and the AVT regimen used was interferon-based. However, these two patients did not achieve SVR. In addition, two (11.8%) of the 17 patients had been under HCC surveillance using USG with serum AFP. However, in these two patients, USG was performed annually, not every

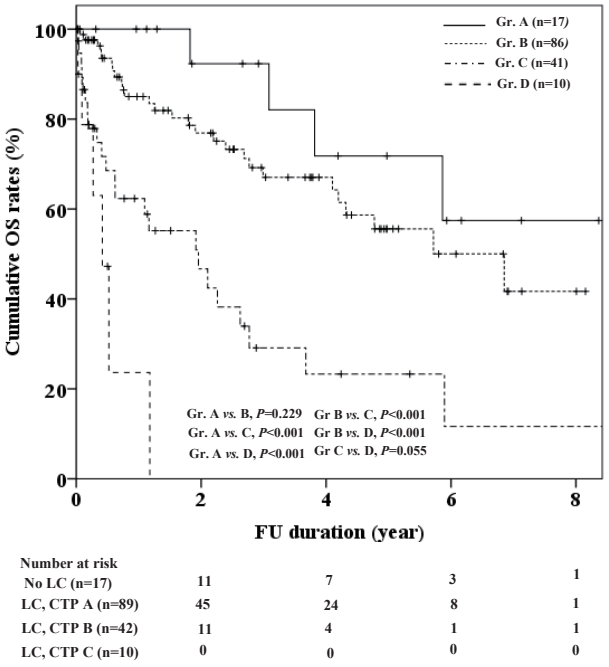

Figure 3. Relations between cumulative overall survivals and Child-Turcotte-Pugh (CTP) class in hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) patients with or without liver cirrhosis. Cumulative overall survival (OS)s were not significantly different between non-cirrhotic and cirrhotic CTP class A patients (P=0.229). However, OSs of HCV-associated HCC patients were better for those of CTP class A, regardless of liver cirrhosis (LC), than for patients with LC of CTP class B or C (P-values for all <0.001). Gr. A, CTP class A patients without LC; Gr. B, CTP class A patients with LC; Gr. C, CTP class B patients with LC; Gr. D, CTP class C patients with LC; FU, follow-up; Gr, group.

6 months, and serum AFP levels were low (2.9 and 13.1 ng/mL, respectively). At diagnosis of HCC, these two patients had no initial symptoms. With regard to tumor characteristics, 10 had a single and 7 had two HCC(s), and median tumor size was 4.2 cm (range, 2.1-8.3 cm). In one of the 17 patients, HCC exhibited portal vein thrombosis (PVT) by tumor invasion, and 10 had HCC within Milan criteria. Twelve, four, and one of the 17 patients had HCCs with BCLC stages A, B, and C, respectively. Interestingly, in case 5, the patient was diagnosed as having HCC with BCLC stage B despite a history of AVT and annual HCC surveillance.

3. OS rates of HCV-associated HCC patients according to the presence of LC

During the follow-up period, 4 of the 17 non-cirrhotic patients died, and 57 of the 137 cirrhotic patients. Median OSs of HCV-associated HCC patients with and without LC were 15 months and 37 months, respectively. The 2-, 4-, and 6-year cumulative OS rates of the non-cirrhotic group were 92.3%, 71.8%, and 57.4%, respectively. And, the 2-, 4-, and 6-year cumulative OS rates of the cirrhotic group were 64.4%, 51.2%, and 35.9%, respectively (P=0.036) (Fig. 2).

In order to identify whether OSs were dependent on the remnant liver function rather than LC *per se*, we compared group OSs according to CTP class between the two groups (Fig. 3). In the non-cirrhotic group, all patients (n=17) were CTP class A (subgroup A), whereas in the cirrhotic group, 86, 41, and 10 patients were of CTP class A (subgroup B), B (subgroup C), and C (subgroup D), respectively. Cumulative

Table 3. Predictors of overall survival of HCV-related HCC patients (n=154)

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (years)	1.01 (0.99-1.03)	0.356	-	-
Sex (male)	1.32 (0.77-2.28)	0.317	-	-
BMI (kg/m^2)	0.94 (0.88-1.01)	0.094	-	-
DM (presence)	0.94 (0.56-1.58)	0.804	-	-
HTN (presence)	0.59 (0.35-1.02)	0.058	-	-
AST (IU/L)	1.00 (1.00-1.01)	0.001	1.01 (1.00-1.01)	0.003
ALT (IU/L)	0.99 (0.99-1.01)	0.588	-	-
AFP (ng/mL)	1.00 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	0.016
LC and CTP class				
No LC (-, CTP A)	Reference	-	-	-
LC (CTP A)	1.85 (0.64-5.28)	0.256	2.06 (0.66-6.45)	0.216
LC (CTP B)	5.68 (1.95-16.56)	0.001	5.24 (1.62-16.92)	0.006
LC (CTP C)	18.01 (4.76-68.10)	<0.001	21.79 (4.27-111.39)	<0.001
AVT (yes vs. no)	0.19 (0.06-0.62)	0.006	0.25 (0.07-0.82)	0.022
Tumor number (multiple vs. single)	1.74 (1.04-2.92)	0.036	1.12 (0.51-2.48)	0.783
Tumor size (cm)	1.21 (1.08-1.36)	0.001	1.13 (0.96-1.33)	0.135
Tm type (diffuse vs. nodular)	4.19 (1.50-11.70)	0.006	1.26 (0.38-4.25)	0.706
BCLC stage (B/C/D vs. 0/A)	3.14 (1.84-5.38)	<0.001	1.18 (0.44-3.17)	0.741
Curative-intended Tx (yes)	0.41 (0.19-0.87)	0.020	0.85 (0.38-1.87)	0.679

Curative-intent treatment: operation or radiofrequency ablation in the present study. Event: death (n=61).
HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, Alpha-fetoprotein; LC, liver cirrhosis; CTP, Child-Turcotte-Pugh classification; AVT, antiviral therapy; BCLC, Barcelona Clinic Liver Cancer; Tx, treatment.

OSs of these 4 subgroups were compared. Between the subgroups A and B, their cumulative OSs were not significantly different (P=0.229). The cumulative OS of the subgroup A was better than those of the subgroups C (P<0.001) and D (P<0.001), respectively, and the cumulative OS of the subgroup B was also better than those of the subgroups C (P<0.001) and D (P<0.001), respectively. The cumulative OS of the subgroup C tended to be higher than that of the subgroup D (P=0.055).

4. Predictors of OS in HCV-associated HCC patients

Mutivariate analysis showed that serum AST (HR 1.01 [CI, 1.00-1.01], P=0.003), serum AFP (HR 1.01 [CI, 1.00-1.01], P=0.016), LC with CTP class B (HR 5.24 [CI, 1.62-16.92], P=0.006), LC with CTP class C (HR 21.79 [CI, 4.27-111.39], P<0.001), and a history of AVT (HR 0.25 [CI, 0.07-0.82], P=0.022), were significantly associated with the prognosis of HCV-associated HCC patients (Table 3).

DISCUSSION

In this study, among 154 HCV-associated HCC patients, only 17 (11.0%) had a non-cirrhotic liver, and all 17 had well preserved liver function (CTP class A). For these 17 patients, the proportion of males, median platelet count, and median albumin level were significantly higher than in the cirrhotic group, and 12 (70.6%) had BCLC A staged HCC. However, tumor number and median tumor sizes were not significantly different for HCV-associated HCC patients with or without LC. OS was significantly greater in the non-cirrhotic group, but not between patients of CTP class A in the two patient groups. Furthermore, the OSs of HCV-associated HCC patients were better for patients of CTP class A, regardless of LC, than for cirrhotic patients of CTP class B or C. Multivariable analyses showed serum AST, AFP, CTP class B, CTP class C, and a history of AVT were significantly associated with OS in our 154 study subjects.

HCC usually develops in cirrhotic livers, but 5-70% of HCCs have been reported to develop in patients with a non-cirrhotic livers.[3,30-32] And, HCV patients without LC are not subject to surveillance according to AASLD or European Association for the Study of the Liver guideline,[22,33] but are subject to surveillance according to Korean Liver Cancer Association-National Cancer Center guideline.[34] Moreover, the incidence of HCC in patients with a non-cirrhotic liver depends on the etiology of chronic liver disease.[3,30,32] In terms of HCV-associated HCCs, several recent studies have reported that 2-68% of HCCs occur in patients with a non-cirrhotic liver.[32,35,36] In the present study, 11.0% of HCV-associated HCC patients were diagnosed without LC, which concurs with previous reports.[32,35,36] However, the cost-effectiveness of HCC surveillance for these patients was not evaluated in the present study, and thus, we do not comment on the need for HCC surveillance in these patients. Nonetheless, our findings caution that HCV-associated HCC occurs uncommonly in the absence of cirrhosis.

In order to identify the features of HCV-associated HCC patients without LC and to determine which HCV patients are more likely to develop HCC in the absence of LC, we compared their clinical features with those of HCV-associated HCC patients with LC. Demographically, HCV-associated HCC in a non-cirrhotic liver was more frequently observed in female patients, which is in-line with a previous study,[17] and suggests that sex hormones may be associated with the development of HCV-associated HCC in a non-cirrhotic liver. However, the mechanism of HCC carcinogenesis in HCV patients without LC remains unclear. In the present study, 11 (64.7%) of the 17 HCV-associated HCC patients without LC were diagnosed incidentally during a medical examination despite the absence of symptoms. Therefore, although such patients are not eligible for the current HCC surveillance program,[28] more attention should be paid to the diagnosis early HCC despite the absence of symptoms in HCV patients without LC.

In the present study, we evaluated the OS of HCV-associated HCC patients according to the presence of LC, and compared OSs with respect to CTP class in those with or without LC. In a previous Korean study, although an OS difference was observed between HCC patients with or without LC, the relation between OS and the cause of chronic liver

disease was not explored, and the majority of subjects enrolled were HBV-associated HCC patients.[37] On the other hand, in the present study, we focused on HCV-associated HCC patients, and found that reserved liver functions in CTP class B or C cases with a cirrhotic liver were significantly associated with poorer OS in HCV-associated HCC patients. However, the non-cirrhotic group did not contain any patient of CTP class B or C, and thus, we could not directly compare OSs of CTP class B or C patients with or without LC. Nonetheless, given that serum levels of albumin or PT are correctable in compensated liver, our findings suggest the correction of liver function before anti-HCC treatment in HCV-associated HCC patients may importantly affect patient's prognosis. In addition, we found OS was significantly better in patients without LC than in those with LC, as expected. However, we need to interpret this results because the numbers of patients without LC and of their event (death) were small as 7 and 4, respectively, and the follow-up period differs significantly between the cirrhotic and non-cirrhotic group. It is a disadvantage of this study.

The goal of AVT in patients with HCV infection is to eradicate of virus and decrease the incidence of HCV-related complications including HCC development and mortality. In the present study, we sought to investigate the effects of AVT for HCV on the development of HCC in HCV patients with and without LC, but unfortunately, we failed to do so as only 22 patients received AVT. HCC occurred in 4 (20%) cirrhotic patients despite the achievement of SVR, but it did not develop in non-cirrhotic patients with SVR. On the other hand, it has been reported that AVT can improve reserve liver function in HBV-associated HCC patients, and may reduce the recurrence rate or delay HCC progression.[38,39] However, the effect of AVT for HCV infection after diagnosis of HCV-associated HCC on OS is not clear. Although several studies have reported risk of HCC development in HCV patients that receive AVT, these study results should be carefully interpreted because liver status at the time of AVT may have confounded the analyses performed in these retrospective, observational studies. Therefore, we suggest a large-scale prospective study be conducted in HCV patients that receive AVT to investigate these issues.

In the multivariate analysis, BCLC stage was a significant factor for OS of the enrolled patients, but it was not an independent prognostic factor for OS, unexpectedly. This may be confounded by treatment type for HCC or the presence of LC. Despite the very early/early staged HCC (BCLC stage 0/A), some patients received TACE or supportive care in the present study, and their prognosis was not optimistic. Similarly, curative-intended treatment could not an independent prognostic factor for OS, and this may be also confounded by the presence of LC. However, these findings need to be validated using large scaled prospective multicenter studies.

This study has several limitations. First, selection bias could not be avoided due to the retrospective design of the present study. Moreover, because of its non-randomized nature, the study is subject to the effects of several confounders although it was conducted on only HCV-associated HCC patients to prevent etiologically-related effects. Therefore, large-scale well designed randomized studies are required. Second, we failed to demonstrate the effects of AVT on HCC development in HCV patients with or without LC due to the small number of patients with a history of AVT and the relatively small number of patients in the non-cirrhotic group. However, in view of the fact that the prevalence of HCV-associated HCC without LC has not been well established in HBV-endemic areas, we hope that our results provide useful information for the follow-up of HCV patients in HBV-endemic areas. Third, due to the retrospective design, we could not confirm LC based on pathologic findings in all enrolled patients.

Summarizing, 11% of HCV-associated HCC patients do not have underlying cirrhotic liver, and all such patients included in this study had well preserved liver function (CTP class A). This suggests that HCV patients without LC may be also at risk of HCC development in HBV-endemic area, such as South Korea. Therefore, the possibility of HCC development in these patients require attention, despite their ineligibilities for the HCC surveillance program. On the other hand, the OSs of HCV-associated HCC patients were better for those of CTP class A, regardless of LC, than cirrhotic patients of CTP class B or C. This finding suggests preserved liver function rather the presence of LC *per se* is associated

with the prognosis of HCV-related HCC patients, and that every effort should be made to preserve liver function in HCV patients.

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AUTHOR CONTRIBUTIONS

J Shin, JH Yu, and YJ Jin were responsible for the concept and design of the study, the acquisition, analysis, and interpretation of data, and drafting of the manuscript. JH Yu and JW Lee helped with data acquisition.

Conflicts of Interest

The authors have no conflict of interest to declare.

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