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Clinical characteristics and prognosis of Korean patients with hepatocellular carcinoma with respect to etiology

Wonjoon Jang[1*], Hye Won Lee[1,2,3*], Jae Seung Lee[1,2,3], Beom Kyung Kim[1,2,3], Seung Up Kim[1,2,3], Jun Yong Park[1,2,3], Sang Hoon Ahn[1,2,3], Do Young Kim[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, [2]Institute of Gastroenterology, Yonsei University College of Medicine, [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea

Background/Aim: The profile of patients with hepatocellular carcinoma (HCC) has changed globally; the role of etiology in predicting prognosis of HCC patients remains unclear. We aimed to analyze the characteristics and prognosis of Korean patients with HCC according to disease etiology.

Methods: This retrospective observational study included patients diagnosed with HCC between 2010 and 2014 in a single center in Korea. Patients with HCC aged <19 years old, had coinfection with other viral hepatitis, had missing follow-up data, were Barcelona Clinic Liver Cancer stage D, or died before 1 month were excluded.

Results: A total of 1,595 patients with HCC were analyzed; they were classified into the hepatitis B virus (HBV) group (1,183 [74.2%]), hepatitis C virus (HCV) group (146 [9.2%]), and non-B non-C (NBNC) group (266 [16.7%]). The median overall survival of all patients was 74 months. The survival rates at 1, 3, and 5 years were 78.8%, 62.0% and 54.9% in the HBV group; 86.0%, 64.0%, and 48.6% in the HCV group; and 78.4%, 56.5%, and 45.9% in the NBNC group, respectively. NBNC-HCC has a poorer prognosis than other causes of HCC. Survival was significantly longer in the HBV group with early-stage HCC than in the NBNC group. Furthermore, survival was shorter in patients with early-stage HCC and diabetes mellitus (DM) than in those without DM.

Conclusions: The etiology of HCC affected clinical characteristics and prognosis to some extent. NBNC-HCC patients showed shorter overall survival than viral-related HCC patients. Additionally, the presence of DM is an additional important prognostic factor in patients with early-stage HCC. **(J Liver Cancer 2022;22:158-166)**

Keywords: Carcinoma, hepatocellular; Etiology; Prognosis; Diabetes mellitus; Survival

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, the sixth most common cancer worldwide, and the fourth leading cause of cancer-related mortality.[1-3] HCC is mainly associated with chronic viral hepatitis including hepatitis B virus (HBV) or hepatitis C

Corresponding author: Do Young Kim

Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel. +82-2-2228-1992, Fax. +82-2-393-6884
E-mail: dyk1025@yuhs.ac

*These two authors contributed equally to this work.

virus (HCV).[4] In South Korea, HBV infection is 65-75% of HCC cases diagnosed, while HCV infection is associated with 8.6-13.2% of cases.[5,6] Recently, non-B non-C (NBNC) HCC has gradually increased and been reported to be 15-18% in Korea.[6]

Various factors influence the development of HCC through different mechanisms.[7] HBV is a DNA-based virus that can be incorporated into the host genome. Random insertions cause chromosomal instability that drives carcinogenesis.[8,9] HCV is an RNA virus that does not integrate into host DNA. Due to the absence of reverse transcription activity of the HCV RNA virus, its viral genome does not integrate into the genome of the infected cell. HCV causes HCC through an indirect pathway by causing chronic inflammation, cell death, proliferation and cirrhosis.[8] In addition, tumorigenesis is associated with non-viral risk factors such as fatty liver disease or heavy alcohol consumption.[10] NBNC population constitutes a substantial proportion of patients with HCC and has become the main cause of liver transplantation.

Most HCC cases develop in patients with cirrhosis. Generally, genetic and epigenetic mechanisms play an important role in the malignant transformation of dysplastic nodules.[11] Given the different etiologies and characteristics of HCC, the prognosis may vary between HBV, HCV, and NBNC patients. However, the earlier results are somewhat controversial. In a recent study, HBV-related patients showed favorable survival compared with other etiologies.[12] Some studies found significant survival differences between groups with different risk factors for HCC,[13-18] while others did not.[19-23] Furthermore, most studies only compared virus-infected groups (HBV vs. HCV) or combined both viral groups when compared to patients with NBNC.

However, the profiles of patients with HCC are changing. Remarkable treatment advances include immunotherapy, tyrosine kinase inhibitor, and transarterial radioembolization, which increase survival and quality of life but remain under evaluation. The NBNC-HCC population is increasing and currently outnumbers the HCV-HCC population in some regions.[24] Therefore, it is crucial to explore the role of etiology in HCC prognosis. In this study, we analyzed the characteristics of patients with HCC and their prognosis according to the etiology of the disease in Korea.

METHODS

1. Study population

Between 2010 and 2014, 1,900 patients who were first diagnosed with HCC at Severance Hospital, Yonsei University College of Medicine, South Korea, were enrolled. HCC was diagnosed histologically or radiologically according to the guidelines of the Korean Liver Cancer Association, American Association for the Study of Liver Disease or the European Association for the Study of the Liver.[23] Patients aged <19 years, those who had coinfection with other viral hepatitis, those who had missing follow-up data, or those who died before 1 month were excluded (Supplementary Fig. 1). Additionally, patients with Barcelona Clinic Liver Cancer (BCLC) stage D were excluded.

The patients were divided according to the etiology of the disease into three groups (HBV, HCV, and NBNC). Patients with HBsAg-positivity for ≥6 months, previous history of chronic HBV infection, and anti-HCV antibody-negative sera were assigned to the HBV group, those with anti-HCV antibody positive and HBsAg-negative sera were assigned to the HCV group. The remaining patients negative for HBV and HCV were assigned to the NBNC group; therefore, this was a heterogeneous group and included those whose HCC was attributable to alcoholic liver disease.

This retrospective observational study followed the STROBE guidelines (Supplementary Table 1). This study adhered to the ethical guidelines of the Declaration of Helsinki (1975). This study was approved by the Severance Hospital Institutional Review Board (IRB No. 4-2020-1081).

2. Variables and outcomes

All clinical, serological, and histological data were obtained from electronic medical records. Clinical variables included age, hypertension, type 2 diabetes mellitus (DM), sex, smoking, alcohol consumption (social drinking), BCLC stage, Child-Pugh score, and initial treatment (transarterial chemoembolization, transarterial radioembolization, radiofrequency ablation, cryoablation, systemic or intra-arterial chemotherapy, radiation,

concurrent chemoradiation, surgical resection, etc.). Computed tomography and magnetic resonance imaging were used to explore tumor size, macrovascular invasion (MVI), and extrahepatic metastasis. We recorded the following serologic variables: albumin, total bilirubin, alpha-fetoprotein (AFP), prothrombin induced by the absence of vitamin K or antagonist-II (PIVKA-II), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and prothrombin time expressed as the international normalized ratio. All data were obtained using routine methods. The primary outcome was

Table 1. Baseline characteristics of patients with hepatocellular carcinoma according to etiology

Variable	Total (n=1,595)	HBV (n=1,183)	HCV (n=146)	NBNC (n=266)	*P*-value
Age (years)	59.0 (52.0-67.0)	57.0 (50.0-64.0)	68.0 (61.8-74.0)	67.0 (60.0-72.0)	<0.001
Male sex	1,263 (79.2)	943 (79.7)	105 (71.9)	215 (80.8)	0.070
Hypertension	524 (32.9)	339 (28.7)	63 (43.2)	122 (45.9)	<0.001
Diabetes	401 (25.1)	237 (20.0)	42 (28.8)	122 (45.9)	<0.001
Smoking	825 (50.3)	607 (51.3)	69 (47.3)	149 (56.0)	0.201
Alcohol	910 (55.2)	658 (55.6)	73 (50.0)	179 (67.3)	<0.001
Child-Pugh score A	1378 (86.4)	1022 (86.4)	125 (85.6)	231 (86.8)	0.942
Child-Pugh score B	217 (13.6)	161 (13.6)	21 (14.4)	231 (86.8)	
Albumin (g/dL)	3.8 (3.3-4.2)	3.8 (3.4-4.2)	3.5 (3.1-3.9)	3.7 (3.3-4.1)	<0.001
Total bilirubin (mg/dL)	0.80 (0.60-1.20)	0.80 (0.60-1.20)	0.70 (0.50-1.00)	0.70 (0.50-1.10)	<0.001
Prothrombin time (INR)	1.04 (0.98-1.11)	1.04 (0.98-1.12)	1.02 (0.96-1.10)	1.02 (0.95-1.10)	0.016
AST (U/L)	46.0 (30.0-76.0)	45.0 (30.0-78.0)	60.0 (41.0-93.3)	39.5 (27.0-63.3)	<0.001
ALT (U/L)	34.0 (23.0-54.0)	36.0 (24.0-58.0)	32.0 (22.0-53.3)	26.0 (18.0-43.0)	<0.001
Tumor size (cm)	3.5 (2.1-6.2)	3.5 (2.1-6.1)	3.3 (1.9-6.4)	3.6 (2.1-6.6)	0.005
Macrovascular invasion	450 (28.2)	355 (30.0)	29 (19.9)	66 (24.8)	0.015
Extrahepatic metastasis	106 (6.6)	177 (15.0)	19 (13.0)	38 (14.3)	0.183
BCLC stage 0	173 (10.8)	130 (11.0)	15 (10.3)	28 (10.5)	0.028
BCLC stage A	570 (35.7)	424 (35.8)	56 (38.4)	90 (33.8)	
BCLC stage B	314 (19.7)	213 (18.0)	41 (28.1)	60 (22.6)	
BCLC stage C	538 (33.7)	416 (35.2)	34 (23.3)	88 (33.1)	
AFP (ng/mL)	21.9 (5.3-364.7)	365 (30.9)	38 (26.0)	59 (22.2)	0.013
PIVKA-II (mAU/mL)	75 (24-1,353)	523 (44.2)	73 (50.0)	138 (51.9)	0.046
Initial treatment					0.004
TACE	695 (43.6)	495 (41.8)	86 (58.9)	114 (42.9)	
Surgical resection	513 (32.2)	407 (34.4)	28 (19.2)	78 (29.3)	
Radiotherapy or CCRT	146 (9.2)	103 (8.7)	10 (6.9)	33 (12.4)	
Chemotherapy	106 (6.6)	84 (7.1)	7 (4.8)	15 (5.6)	
RFA or cryoablation	76 (4.8)	50 (4.2)	8 (5.5)	18 (6.8)	
TARE	49 (3.1)	36 (3.0)	6 (4.1)	7 (2.6)	
Liver transplantation	10 (0.6)	8 (0.7)	1 (0.7)	1 (0.4)	

Values are expressed as n (%) or median (interquartile range).
AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CCRT, concurrent chemoradiotherapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; NBNC, non-B non-C; PIVKA-II, prothrombin induced by the absence of vitamin K or antagonist-II; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

overall survival (OS), determined from the date of initial diagnosis to death or the last follow-up date.

3. Statistical methods

Pearson's chi-square test was used to compare baseline categorical variables. Analysis of variance or the Kruskal–Wallis test was used to compare continuous variables. OS was calculated using the Kaplan–Meier method. The association between each baseline variable and survival was tested using univariate analysis (log-rank test). Significant variables (P<0.05) in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed with SPSS software ver. 22.0 (SPSS Inc, Chicago, IL, USA). Two-sided P<0.05 were considered statistically significant.

RESULTS

1. Baseline characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. Finally, 1,595 patients with HCC were analyzed. Of the 1,595 patients, 1,183 (74.2%) were in the HBV group, 146 (9.2%) were in the HCV group, and 266 (16.7%) were in the NBNC group. The HCV group had the highest proportion of female patients. The NBNC group had more elderly patients and metabolic comorbidities, including hypertension or type 2 DM than the viral hepatitis group. The HCV group had the lowest serum albumin level (3.5 g/dL vs. 3.8 g/dL and 3.7 g/dL, P<0.001) and the highest AST level (60.0 U/L vs. 45.0 U/L and 39.5 U/L, P<0.001) compared to the HBV and NBNC groups. The HBV group had the highest ALT level (36.0 U/L) compared to the HCV group (32.0 U/L) and the NBNC group (26.0 U/L)

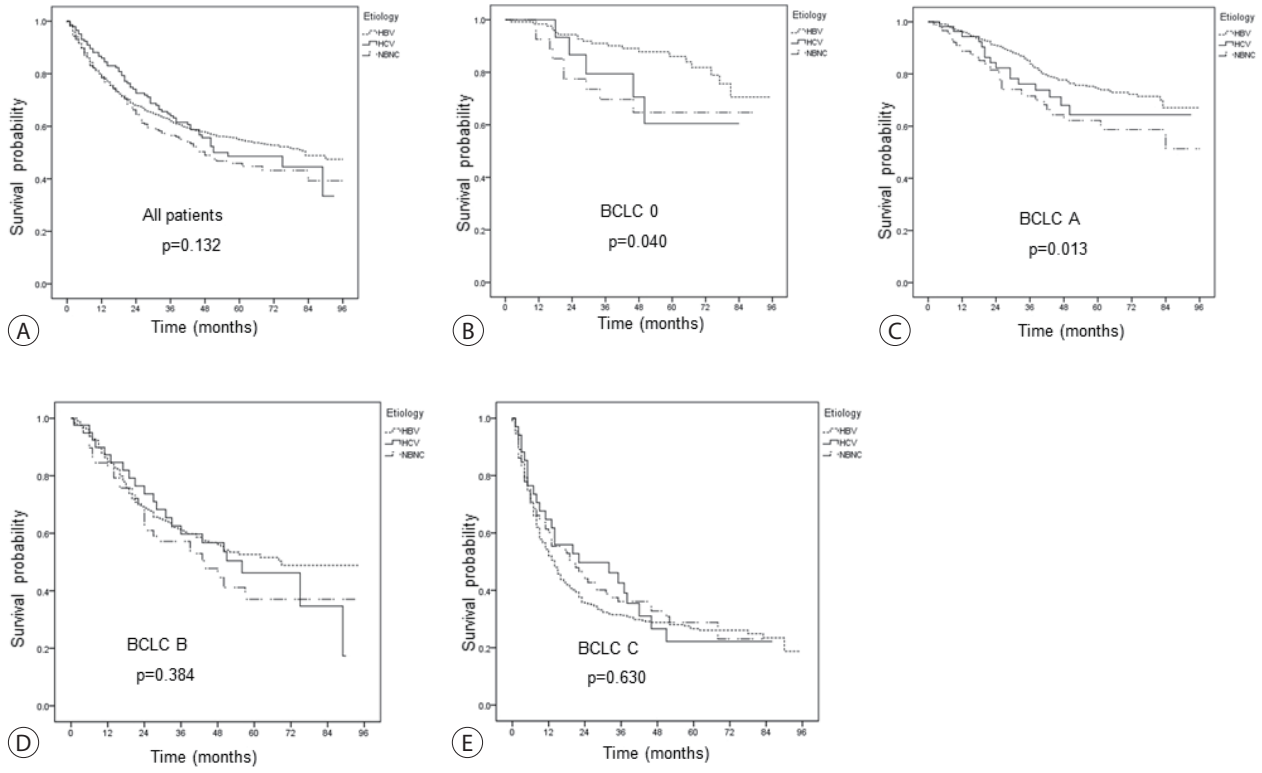

Figure 1. Overall survival of patients with hepatocellular carcinoma according to cancer etiology and Barcelona Clinic Liver Cancer (BCLC) stages. (A) All patients (log-rank, P=0.132), (B) BCLC stage 0 patients (log-rank, P=0.040), (C) BCLC stage A (log-rank, P=0.013), (D) BCLC stage B patients (log-rank, P=0.384), and (E) BCLC stage C patients (log-rank, P=0.630). HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C.

(P<0.001).

The NBNC group had the largest mean tumor size (3.6 cm vs. 3.5 cm in the HBV group and 3.3 cm in the HCV group, P=0.005). MVI was the least common in the HCV group (19.9% vs. 30.0% in the HBV group and 24.8% in the NBNC group, P=0.015). However, the extrahepatic metastasis rate did not differ between the three groups. The proportion of BCLC stage C patients was lower in the HCV group (23.3%) than in the HBV (35.2%) and NBNC groups (33.1%). The most common initial treatment in all groups was transarterial chemoembolization, followed by surgical resection.

2. OS according to the etiology

The median OS of all patients was 74 months. The survival rates at 1, 3, and 5 years were 78.8%, 62%, and 54.9% in the HBV group; 86.0%, 64.0%, and 48.6% in the HCV group; and 78.4%, 56.5%, and 45.9% in the NBNC group, respectively, and were comparable between the groups (Fig. 1A). However, in the BCLC stage 0 or A subgroup, HBV patients had significantly longer OS than NBNC patients (Fig. 1B-E).

3. Risk factors for mortality in patients with HCC

The log-rank test was used to identify factors that predicting prognosis. Univariate analysis identified the following factors: NBNC etiology, albumin, total bilirubin, prothrombin time, AST, tumor size, MVI, extrahepatic metastasis, AFP, and PIVKA-II (Table 2). Factors with P<0.05 were included in the multivariate analysis, which identified the following significant risk factors for mortality: NBNC etiology (hazard ratio [HR], 1.245; 95% confidence interval [CI],

Table 2. Risk factors for mortality in patients with hepatocellular carcinoma

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Etiology						
HBV	Ref					
HCV	1.027	0.795-1.327	0.839			
NBNC	1.217	1.003-1.477	0.046	1.245	1.020-1.518	0.031
Age (years)	1.005	0.997-1.012	0.213			
Male sex	1.016	0.849-1.215	0.866			
Hypertension	1.086	0.930-1.268	0.295			
Diabetes	1.177	0.997-1.389	0.054			
Smoking	1.030	0.887-1.196	0.702			
Alcohol	1.071	0.921-1.246	0.370			
Albumin (g/dL)	0.560	0.495-0.634	<0.001	0.629	0.538-0.734	<0.001
Total bilirubin (mg/dL)	1.087	1.043-1.133	<0.001	1.018	0.967-1.071	0.494
Prothrombin time (INR)	5.546	3.461-8.888	<0.001	2.314	1.280-4.182	0.005
AST (U/L)	1.000	1.000-1.001	0.008	0.999	0.998-1.000	0.260
ALT (U/L)	1.000	0.999-1.001	0.941			
Tumor size (cm)	1.029	1.010-1.049	0.003	1.012	0.992-1.032	0.249
Macrovascular invasion	3.292	2.833-3.825	<0.001	2.682	2.278-3.158	<0.001
Extrahepatic metastasis	4.460	3.550-5.603	<0.001	2.882	2.233-3.720	<0.001
AFP (ng/mL)	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	<0.001
PIVKA-II (mAU/mL)	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	<0.001

HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; PIVKA-II, prothrombin induced by the absence of vitamin K or antagonist-II; HR, hazard ratio; 95% CI, 95% confidence interval; Ref, reference.

1.020-1.518; *P*=0.031), low albumin level (HR, 0.629; 95% CI, 0.538-0.734; *P*<0.001), high prothrombin time (HR <2.314; 95% CI, 1.280-4.182; *P*=0.005), MVI (HR, 2.682; 95% CI, 2.278-3.158; *P*<0.001), extrahepatic metastasis status (HR, 2.882; 95% CI, 2.233-3.720; *P*<0.001), high AFP (HR, 1.000; 95% CI, 1.000-1.000; *P*<0.001), and PIVKA-II (HR, 1.000; 95% CI, 1.000-1.000; *P*<0.001) levels (Table 2). We also analyzed the risk factors for mortality in each stage of BCLC (Supplementary Tables 2-5).

4. The effects of DM on the risk of mortality

We explored the effect of type 2 DM on OS (Fig. 2A). Overall, DM was a risk factor for mortality in patients with early-stage HCC, including BCLC stage 0 or A, but not B or C (Fig. 2B-D). Similar results were obtained when the HBV and NBNC sub-groups were analyzed (Table 3). DM increased the risk of mortality in HCC patients with BCLC 0 (HR, 2.06; 95% CI, 1.00-4.22; *P*=0.049) and BCLC A (HR, 1.65; 95% CI, 1.17-2.31; *P*=0.004) in overall population. In HBV-HCC and NBNC-HCC only, DM similarly increased the risk of mortality in HCC patients with BCLC 0 (HR,

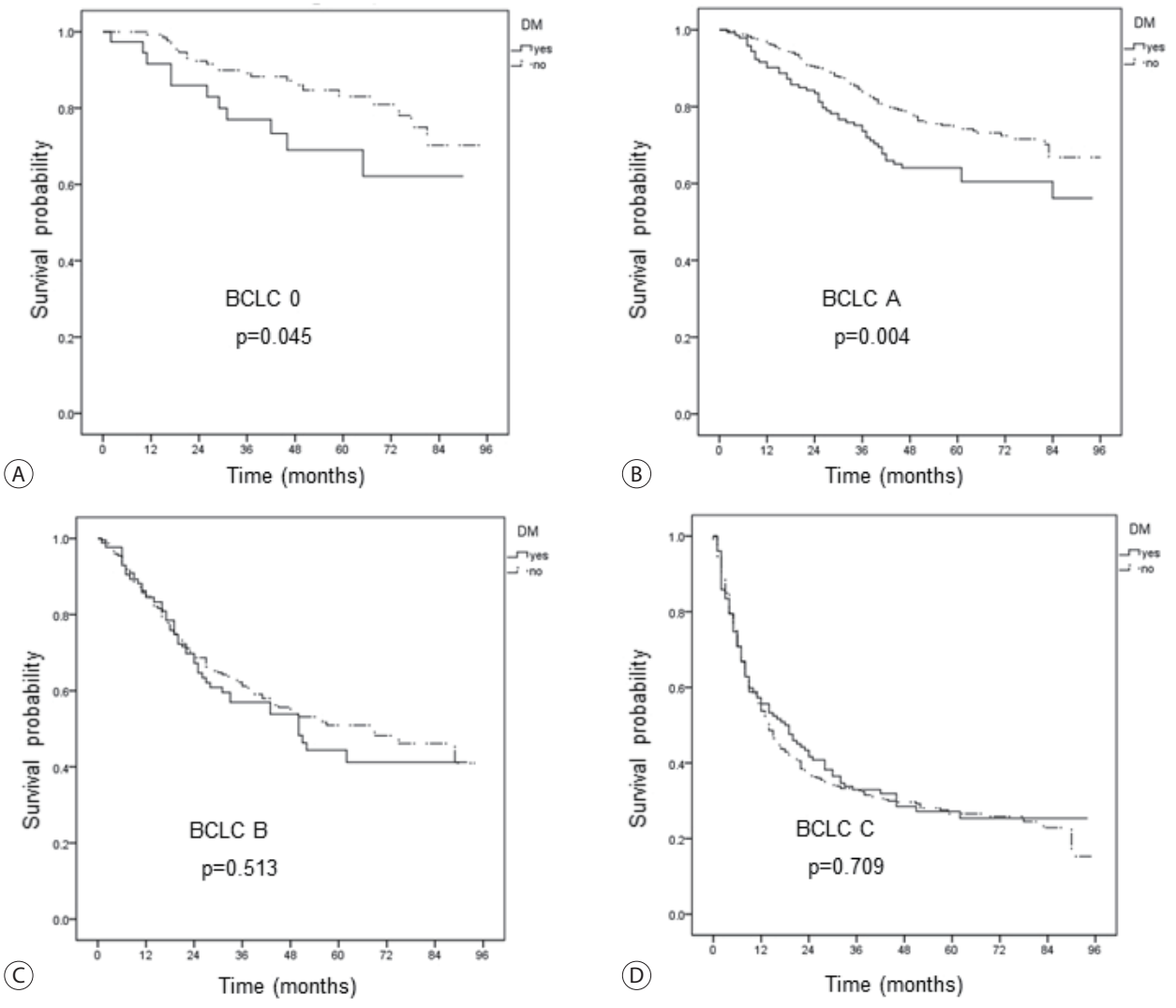

Figure 2. Survival of patients with hepatocellular carcinoma with different Barcelona Clinic Liver Cancer (BCLC) stages with or without diabetes mellitus. (A) BCLC stage 0 patients (*P*=0.045), (B) BCLC stage A patients (*P*=0.004), (C) BCLC stage B patients (*P*=0.513), (D) BCLC stage C patients (*P*=0.709).

Table 3. The effect of diabetes mellitus on mortality in patients with hepatocellular carcinoma

BCLC	DM	Overall population		HBV-HCC and NBNC-HCC only	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Stage 0	No	Ref			
	Yes	2.06 (1.00-4.22)	0.049	2.97 (1.40-6.30)	0.005
Stage A	No	Ref			
	Yes	1.65 (1.17-2.31)	0.004	1.78 (1.25-2.53)	0.002
Stage B	No	Ref			
	Yes	1.13 (0.79-1.61)	0.508	1.00 (0.68-1.50)	0.979
Stage C	No	Ref			
	Yes	0.96 (0.75-1.21)	0.713	0.97 (0.75-1.24)	0.782

BCLC, Barcelona Clinic Liver Cancer; DM, diabetes mellitus; HR, hazard ratio; 95% CI, 95% confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NBNC, non-B non-C; Ref, reference.

2.97; 95% CI, 1.40-6.30; *P*=0.005) and BCLC A (HR, 1.78; 95% CI, 1.25-2.53; *P*=0.002) in overall population.

DISCUSSION

We explored whether the etiology of HCC affected disease characteristics and prognosis. As previously reported, we found that the mean age of HCV and NBNC patients was approximately 10 years older than that of HBV patients.[14,16,21] The NBNC group had the lowest serum AST and ALT levels. Although liver enzyme levels differed between the groups, the Child–Pugh score, liver function, and prognosis did not show differences. The tumor size was the largest in the NBNC group. The frequency of MVI was the highest in the HBV group. When the groups were evaluated in terms of extrahepatic metastasis, BCLC stage distribution, and initial treatment, the aggressiveness of HCC did not show differences between the groups. The HBV group had significantly longer OS than the NBNC group in HCC patients with early stage. Therefore, we stratified the patients according to BCLC stage and found that HBV patients with BCLC stages 0 and A (but not B or C) survived significantly longer than those with NBNC. However, this should be interpreted with caution, as the proportion of patients with DM in the NBNC group was more than twice that of the HBV group.

We also speculate that DM may affect survival differently according to the HCC stage. The results of the univariate analysis, shown in Table 3 and Fig. 2, support this conclusion. DM was a significant independent predictor of poorer survival in patients with BCLC stages 0 and A, but not B or C. Others have reported that DM in patients with HCC is a prognostic factor. One study from Taiwan found that DM was a crucial predictor of survival in patients with early-stage HCC (BCLC 0 and A).[25] DM can enhance or reduce survival depending on the BCLC stage or treatment.[25-27] We did not consider other confounders (metabolic syndrome or insulin resistance) that could contribute to the apparent difference in survival between the HBV and NBNC groups.

A limitation of our study is that the etiologies of NBNC may have differed; they had either non-alcoholic fatty liver disease or alcoholic liver disease. Therefore, we were unable to explain the difference in survival rates between the HBV and NBNC groups. In addition, we did not have information on the cause of death; therefore, we could not distinguish liver-related death due to cancer from other causes. This would have helped to determine whether the high mortality rate in NBNC patients with early-stage cancer was attributable to DM. In addition, we used it as a prognostic indicator. Further studies should consider recurrence-free survival, progression-free survival, tumor response, and quality of life.[28] Finally, there were more patients in the HBV group than in the other groups. We initially considered using propensity score matching, but we would have lost a great deal of data if we had used method. Therefore, we decided to preserve the

entire dataset.

In conclusion, the etiology of HCC affected clinical characteristics and prognosis to some extent. NBNC-HCC patients showed shorter OS than viral-related HCC patients. Additionally, the presence of DM is an additional important prognostic factor in patients with early-stage HCC.

Conflict of Interest

Hye Won Lee currently serves on the editorial board of J Liver Cancer. She was not involved in the review process of this article. Otherwise, the authors have no conflicts of interest to disclose.

Ethics Statement

This study adhered to the ethical guidelines of the Declaration of Helsinki (1975). This study was approved by the Severance Hospital Institutional Review Board (IRB No. 4-2020-1081). The need for informed consent was waived due to the retrospective nature of this study.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

ORCID

Wonjoon Jang	https://orcid.org/0000-0003-3871-8475
Hye Won Lee	https://orcid.org/0000-0002-3552-3560
Jae Seung Lee	https://orcid.org/0000-0002-2371-0967
Beom Kyung Kim	https://orcid.org/0000-0002-5363-2496
Seung Up Kim	https://orcid.org/0000-0002-9658-8050
Jun Yong Park	https://orcid.org/0000-0001-6324-2224
Sang Hoon Ahn	https://orcid.org/0000-0002-3629-4624
Do Young Kim	https://orcid.org/0000-0002-8327-3439

Author Contribution

Conceptualization: DYK
Data acquisition: HWL, JSL, BKK, SUK, JYP, SHA, DYK
Data analysis and interpretation: WJJ, HWL, DYK
Writing – original draft: WJJ, HWL, DYK
Writing – review & editing: WJJ, HWL, DYK
Statistical analysis: WJJ, HYL, DYK
Study supervision: DYK
Approval of final manuscript: all authors

Supplementary Material

Supplementary data can be found with this article online https://doi.org/10.17998/jlc.2022.09.18.

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