

Comparison of survival outcomes of alcohol-related hepatocellular carcinoma with or without liver cirrhosis; a ten-year experience

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Abstract

We evaluated overall survivals (OSs) of alcohol-related hepatocellular carcinoma (HCC) patients without LC compared to those with LC.

Between 2005 and 2015, 1343 patients were initially diagnosed as having HCC in our hospital. Of these, 186 alcohol-related HCC patients were enrolled in this study, and their medical records were retrospectively analyzed. Significant alcohol intake was defined as more than 210 grams/week for men and more than 140 grams/week for women.

Non-cirrhotic HCC was observed in 37.1% of the 186 patients. Cumulative OS rates were significantly higher in non-cirrhotic patients ($P = .006$). For the 117 cirrhotic patients, cumulative OS rate was significantly higher in the CTP class A patients than in the CTP class B ($P < .001$) or CTP class C ($P < .001$) patients, respectively. In the 69 non-cirrhotic patients, cumulative OS rate was significantly higher in the CTP class A patients than in the CTP class C patients ($P < .001$), but, not than in the CTP class B patients ($P = .157$). Multivariate analyses revealed that CTP class B ($P < .001$), CTP class C ($P < .001$), and tumor size ($P = .006$) were significant predictors for OS in cirrhotic patients, and that CTP class C ($P = .002$) and tumor size ($P = .023$) were significant predictors for OS in non-cirrhotic patients.

OS was found to be better for non-cirrhotic than cirrhotic patients with alcohol-related HCC. Survivals of alcohol-related HCC patients without cirrhosis were comparable between patients with CTP class A and B.

Abbreviations: AFP = alpha-fetoprotein, ALD = alcoholic liver disease, ALT = alanine aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BMI = body mass index, CI = confidence interval, CTP = Child-Turcotte Pugh, DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, LC = liver cirrhosis, NASH = nonalcoholic steatohepatitis, OS = overall survival, RCT = randomized controlled trial.

Keywords: child-turcotte pugh class, cirrhosis, hepatocellular carcinoma, non-cirrhosis, overall survival

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.^[1] About 70% to 90% of HCCs develop in an established background of liver cirrhosis (LC) or of chronic liver disease, such as hepatitis B virus (HBV), hepatitis C virus (HCV),

alcoholic liver disease (ALD), or nonalcoholic steatohepatitis (NASH).^[2–5] Recently, the incidence of HCC attributable to HBV or HCV is expected to be reduced by the gradual generalization of HBV vaccination^[6] and by the use of highly effective anti-HBV and anti-HCV drugs.^[7–9] However, patients with ALD may have an increased share of the cause of HCC,^[2–4] because Alcohol consumption is still high throughout the world. Currently, ALD patients only with LC enter into HCC surveillance program,^[10] but ALD patient without LC should not be overlooked with regard to the occurrence of HCC because some of these patients can also develop HCC.

Clinically, HCC is rarely symptomatic in early stages, and symptoms usually occur with LC in advance staged tumor.^[11,12] Thus, it is important to detect HCC before the onset of symptoms and at a stage without cirrhosis. For this, it is needed to know the clinical characteristics of HCC without cirrhosis well. Some previous studies compared the clinical characteristics and prognosis of ALD patients with or without LC,^[13–16] but most were limited due to small number of ALD patients without LC, and were conducted in Western populations. Recently, a retrospective cohort study reported etiology and clinical features of non-cirrhotic HCC,^[17] but the prognostic factors of overall survival (OS) were not determined in ALD patients without LC. To date, moreover, the clinical characteristics and survival outcomes of HCC in ALD patients without LC compared to those with LC have not been fully evaluated.

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In the present study, therefore, we retrospectively analyzed survival outcomes of HCC in ALD patients without LC compared to those with LC. In addition, the OSs of these patients were comparatively assessed according to Child-Turcotte Pugh (CTP) classification, and prognostic factors of their survival were also evaluated.

2. Patients and methods

2.1. Study subjects

Between 2005 and 2015, 1343 patients were initially diagnosed as having HCC in our hospital. Patients with a treatment history of HCC at other institutions before visiting our hospital were not enrolled. HCC was diagnosed according to the issue of American Association for the Study of Liver Diseases (AASLD) guideline.^[10] Based on this guideline, most HCCs were diagnosed radiologically in this study, without the necessity for biopsy if the typical imaging features for HCC were present on dynamic contrast-enhanced computed tomography (CT)-scan or magnetic resonance imaging (MRI). In case of atypical radiologic findings for HCC, percutaneous liver biopsy was applied, and 9 ($n=4.8\%$) of 186 enrolled patients were diagnosed as having HCC by liver biopsy. Of these 1343 patients, 24 patients with other combined malignancies were excluded, and as were 1133 patients with hepatitis B virus ($n=869$), HCV ($n=135$), non-alcoholic fatty liver disease ($n=55$), primary biliary cirrhosis ($n=2$), or cryptogenic disease ($n=72$) were also excluded. Eventually, 186 patients with alcohol-associated HCC were enrolled in this retrospective cohort, and were serologically negative for Hepatitis B surface antigen (HBsAg) or HCV antibody. The medical records of these subjects were retrospectively analyzed. Although debatable, significant alcohol intake was defined as more than 210 grams/week for men and more than 140 grams/week for women.^[18,19] LC was clinically diagnosed based on the presence of portal hypertension (encephalopathy, esophageal varices, ascites, or splenomegaly, or a low ($<100,000/\text{mm}^3$) platelet count),^[20] or by radiologic findings of ultrasonography, CT, or MRI.^[21,22] This study was approved by the Institutional Review Board of the Inha University Hospital, Incheon, South Korea (Approval number: INHAUH 2017-09-001).

2.2. Statistical analyses

The primary endpoint of this study was OS rate of alcohol-associated HCC patients according to the presence of LC at the initial time of HCC diagnosis. For survival analysis of study subjects, follow-up durations were calculated from the date of initial diagnosis of HCC to the date of death or to April 31, 2017. Median follow-up duration in this study was 11.8 months (range, 0.1–101.6 months). The secondary endpoints were OS rate of these patients according to CTP classification or median tumor size at the initial time of HCC diagnosis, and significant predictive factors of OS.

The clinical characteristics of patients or HCCs were described as medians (ranges) for continuous variables, and numbers (percentages) for categorical variables. The *Chi*-square test, Fisher exact test, or the Student *t* test were used to determine the significances of differences between categorical or continuous variables. Kaplan–Meier analysis was used to evaluate cumulative OS, and groups were compared using the log-rank test. In multivariate analyses, hazard ratios (HRs) and corresponding

95% confidence interval (CI) were estimated using Cox proportional hazards regression analysis to determine predictors of OS. Predictors for OS of study subjects were evaluated at the time of initial HCC diagnosis. These factors included age, gender, body mass index (BMI), presence of diabetes mellitus (DM) or hypertension, alanine aminotransferase (ALT), CTP class, tumor size and type, and alpha-fetoprotein (AFP). The statistical analysis was performed using SPSS v19.0 (SPSS Inc, Chicago, IL). Two-tailed *P* values of $<.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of patients are shown in Table 1. Of the 186 ALD-associated HCC patients, 117 (62.9%) and 69 (37.1%) had or did not have LC, respectively. Of the 186 patients, median age was 64 years (range, 38–92 years), and 177 (95.2%) were male. Median BMI was 22.9 kg/m² (range, 14.9–46.8 kg/m²). DM and hypertension were present in 69 (37.1%) and 52 (28.0%), respectively. CTP class A, B, and C were observed in 105 (56.5%), 60 (32.3%), and 21 (11.3%), respectively. Most (98.4%) HCCs were of the nodular type, and 108 (58.1%) had single HCC. Median tumor size was 3.4 cm (range, 1.0–24.0 cm). BCLC stages 0, A, B, C, and D were found in 20 (10.8%), 77 (41.4%), 24 (12.9%), 44 (23.7%), and 21 (11.3%) patients, respectively. Median follow-up duration was 11.8 months (range, 0.1–101.6 months). Between HCC patients with and without LC, median albumin level ($P<.001$), frequency of CTP class A ($P<.001$), and median tumor size ($P=.048$), were significantly higher in HCC patients without LC, whereas median total bilirubin level ($P=.012$) and PT ($P<.001$) were significantly lower in those without LC. Single HCC tended to be frequent in those without LC than in those with LC ($P=.068$). In terms of initial treatment, curative-intent treatments such as surgery and radiofrequency ablation (RFA) tended to be applied more frequently in patients without LC compared to those with LC ($P=.065$). Other variables were not significantly different between HCC patients with and without LC (*P* values for all $>.05$).

3.2. OS rates of ALD-associated HCC patients according to the presence of LC, CTP class, and tumor size

The 2-, 4-, 6-, and 8-year cumulative OSs of the 69 ALD-associated HCC patients without LC were significantly greater than those of the 117 with LC (69.0%, 55.5%, 40.7%, 40.7% vs 51.5%, 33.6%, 20.8%, 4.2%, respectively, $P=.006$) (Fig. 1).

In 117 ALD-associated HCC patients with LC, the cumulative OS rates of patients with CTP class A were significantly greater than those of CTP class B ($P<.001$) and C ($P<.001$) patients, respectively (Fig. 2A), but no significant difference was observed between CTP class B and C ($P=.283$) patients (Fig. 2A). For these 117 patients with LC, median tumor size was 2.8 cm, and therefore, these patients were dichotomized using this value as a cut-off. Cumulative OS rates of patients with a tumor size of ≤ 2.8 cm were found to be significantly higher than those of patients with a tumor size of > 2.8 cm ($P<.007$) (Fig. 2B).

In 69 ALD-associated HCC patients without LC, cumulative OS rates of with CTP class C patients were significantly lower than those of CTP class A ($P<.001$) and B ($P=.003$) patients,

Table 1
Baseline clinical characteristics of the ALD-associated HCC study subjects.

Variables	Total (n = 186)	With LC (n = 117)	Without LC (n = 69)	P [‡]
Age (years)*	64 (38–92)	63 (38–92)	66 (41–86)	.118
Gender (male), n (%)	177 (95.2)	112 (95.7)	65 (94.2)	.728 [§]
BMI (kg/m ²)*	22.9 (14.9–46.8)	23.2 (14.9–46.8)	22.6 (17.0–31.2)	.232
DM, n (%)	69 (37.1)	45 (38.2)	24 (34.8)	.616
Hypertension, n (%)	52 (28.0)	35 (29.9)	17 (24.6)	.439
ALT (IU/L)	33 (4–449)	33 (8–302)	31 (4–449)	.828
Albumin (mg/dL)*	3.4 (1.9–5.1)	3.1 (1.9–4.8)	3.7 (2.2–5.1)	<.001
T-bil.(mg/dL)*	1.1 (0.2–38.0)	1.3 (0.3–38.0)	0.8 (0.2–12.7)	.012
PT, INR*	1.2 (0.9–3.3)	1.2 (0.9–3.3)	1.1 (0.9–2.8)	<.001
CTP, A/B/C, n (%)	105/60/21 (56.5/32.3/11.3)	52/46/19 (44.4/39.3/16.2)	54/14/2 (76.8/20.3/2.9)	<.001 [§]
AFP (ng/mL)*	15.8 (1.0–6.1x10 ⁴)	12.8 (1.2–6.1x10 ⁴)	20.0 (1.0–6.1x10 ⁴)	.887
Tumor type, n (%)	183/3 (98.4/1.6)	114/3 (97.4/2.6)	69/0 (100/0)	.296 [§]
nodular/diffuse				
Tumor number,				
1/2/3/≥4, n (%)	108/17/11/50 (58.1/9.1/5.9/26.9)	62/14/9/32 (53.0/12.0/7.7/27.4)	46/3/2/18 (66.7/4.3/2.9/26.1)	.129 [§]
1/≥2, n (%)	108/78 (58.1/41.9)	62/55 (65/47)	46/23 (66.7/33.3)	.068
Tumor size, cm*	3.4 (1.0–24.0)	2.8 (1.0–24.0)	4.6 (1.0–20.0)	.048
BCLC stage, 0/A/B/C/D, n (%)	20/77/24/44/21 (10.8/41.4/12.9/23.7/11.3)	11/47/15/25/19 (9.4/40.2/12.8/21.4/16.2)	9/30/9/19/2 (13.0/43.5/13.0/27.5/2.9)	.060 [§]
Initial treatment				.036 [§]
operation	27 (14.5)	11 (9.4)	16 (23.2)	
RFA	11 (5.9)	8 (6.8)	3 (4.3)	
TACE	77 (41.4)	52 (44.4)	25 (36.2)	
Nexavar	4 (2.2)	1 (0.9)	3 (4.3)	
CTx	10 (5.4)	4 (3.4)	6 (8.7)	
RTx	6 (3.2)	5 (4.3)	1 (1.4)	
Supportive care	51 (27.5)	36 (30.8)	15 (21.7)	
Curative-intent tx.†	37 (19.9)	18 (15.4)	19 (27.5)	.045
FU duration (mo)*	11.8 (0.1–101.6)	9.9 (0.1–101.6)	14.4 (0.1–100.6)	.313

AFP=Alpha-fetoprotein, ALD=alcoholic liver disease, ALT=alanine aminotransferase, BCLC=Barcelona clinic liver cancer, BMI=body mass index, CTP=Child-Turcotte-Pugh classification, CTx=chemotherapy, DM=diabetes mellitus, FU=follow-up, HTN=hypertension, LC=liver cirrhosis, mo=month, PT=prothrombin time, RFA=radiofrequency ablation, RTx=radiotherapy, TACE=transarterial chemoembolization, T-bil=total bilirubin, tx=treatment.

* median (range).

† curative-intent treatment: operation or radiofrequency ablation.

‡ P values were calculated using the t test, chi-square test.

§ Fisher-Exact test.

respectively (Fig. 3A), but were not significantly different between CTP class A and B patients ($P=.157$) (Fig. 3A). For these 69 patients without LC, median tumor size was 4.6 cm, and thus, patients were dichotomized using a cut-off of 4.6 cm. The cumulative OS rates of patients with a tumor of ≤ 4.6 cm were significantly greater than those with a tumor size of < 4.6 cm ($P<.007$) (Fig. 3B).

3.3. OS rates of ALD-associated HCC patients with and without LC according to BCLC stage

For all study subjects, the cumulative OS rates of patients with BCLC stage 0 were significantly greater than those with BCLC stages A ($P=0.037$), B ($P=0.003$), C ($P<.001$), or D ($P<.001$) (Fig. 4A). The cumulative OS rates of patients with BCLC stage A were significantly greater than those of patients with BCLC stage C ($P<.001$) or D ($P<.001$) (Fig. 4A). Moreover, the cumulative OS rates of ALD-associated patients treated with curative-intent therapy were significantly greater than those not so treated ($P<.001$) (supplementary Fig. 1A, <http://links.lww.com/MD/D364>)

In the 117 ALD-associated HCC patients with LC, the cumulative OS rates of patients with BCLC stage 0 were

significantly greater than those of patients with BCLC stage B ($P=.014$), C ($P=.001$), or D ($P=.001$) (Fig. 4B). The cumulative OS rates of patients with BCLC stage A were significantly greater than those with BCLC stages B ($P=.039$), C ($P<.001$), or D ($P<.001$) (Fig. 4B), and the cumulative OS rates of cirrhotic patients treated with curative-intent therapy were significantly greater than those not so treated ($P=.002$) (supplementary Fig. 1B, <http://links.lww.com/MD/D364>)

In the 69 ALD-associated HCC patients without LC, the cumulative OS rates of patients with BCLC stage 0 were significantly greater than those of patients with BCLC stage C ($P=.002$) or D ($P=.002$) (Fig. 4C). The cumulative OS rates of patients with BCLC stage A were significantly greater than those of patients with BCLC stage B ($P=.010$), C ($P=.007$), or D ($P<.001$) (Fig. 4C). However, no significant difference between OS rates was observed in non-cirrhotic patients treated with or without curative-intent therapy ($P=.133$) (supplementary Fig. 1C, <http://links.lww.com/MD/D364>). Moreover, subgroup analysis of patients treated with curative-intent therapy ($n=38$) showed that OS rates were similar for patients with or without LC ($P=.743$) (supplementary Fig. 1D, <http://links.lww.com/MD/D364>).

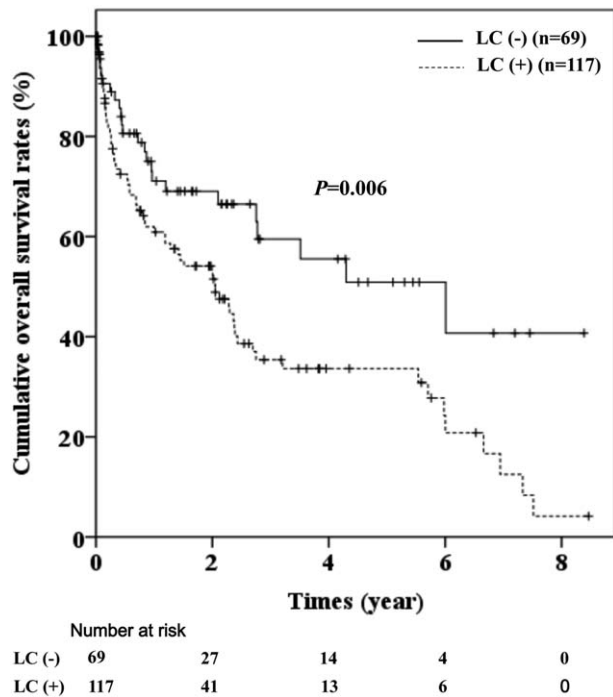


Figure 1. Cumulative overall survivals according to the presence of liver cirrhosis. The cumulative overall survivals of ALD-associated hepatocellular carcinoma patients without liver cirrhosis were significantly better than those with liver cirrhosis ($P = .006$). ALD, alcoholic liver disease. ALD = alcoholic liver disease.

3.4. Predictors of OS in ALD-associated HCC patients with or without LC

In ALD-associated HCC patients with LC, multivariate analysis showed that CTP class B (HR 3.55, $P < .001$), CTP class C (HR 5.67, $P < .001$), tumor size (HR 1.11, $P = .006$), and curative-intent treatment (HR 0.45, $P = .048$) were independent predictors for OS (Table 2). In ALD-associated HCC patients without LC, multivariate analysis showed that CTP class C (HR 16.42, $P = .002$) and tumor size (HR 1.11, $P = .023$) were independent predictors for OS (Table 3).

4. Discussion

In this study, it was found that about 37% of ALD-associated HCC patients developed in non-cirrhotic liver, and OS was significantly better in those without LC than in those with LC. Furthermore, reserve liver function with CTP class A was better in those without LC. Interestingly, median tumor size was larger in those without LC, and curative-intent treatment was more frequently adopted for those without LC than in those with LC. Multivariate analyses showed that moderate- or poor-reserve liver function with CTP class B or C, large tumor size, and non-curative-intent treatment were poorer prognostic factors for OS in alcohol-associated HCC patients with LC. On the other hand, in ALD-associated HCC patients without LC, a large tumor size and poor-reserve liver function with CTP class C were found to be poorer prognostic factors for OS.

Generally, HCC occurs in cirrhotic livers,^[5,23] but about 5% to 70% of HCC cases can also develop in the absence of cirrhosis, and the incidence of HCC in the absence of cirrhosis is vary

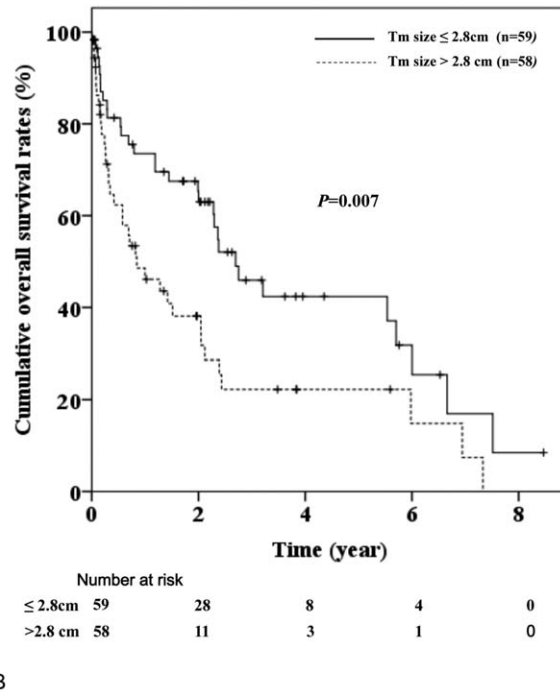
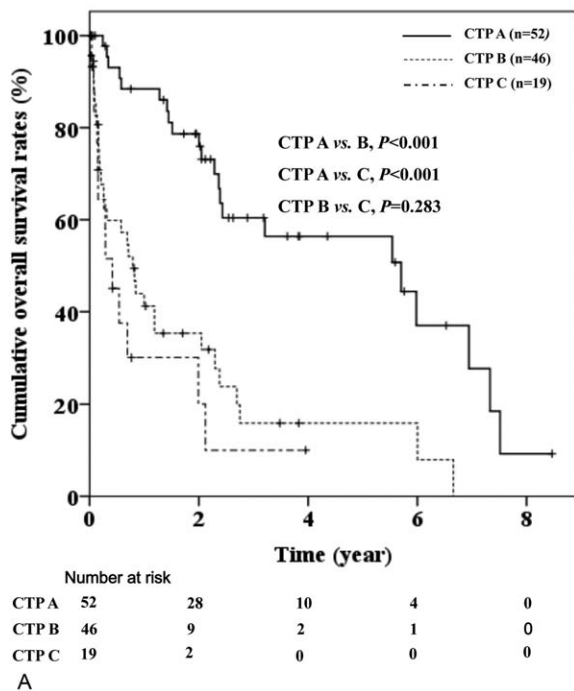


Figure 2. Cumulative overall survivals by CTP class and median tumor size in ALD-associated HCC patients with liver cirrhosis. The cumulative OS rates of patients with CTP class A were significantly higher than those of patients with CTP class B ($P < .001$) or C ($P < .001$) (A). The cumulative OS rates of patients with a HCC tumor of ≤ 2.8 cm were significantly higher than those of patients with a tumor size of > 2.8 cm ($P < .007$) (B). ALD = alcoholic liver disease, CTP = Child-Turcotte-Pugh, HCC = hepatocellular carcinoma, OS = overall survival.

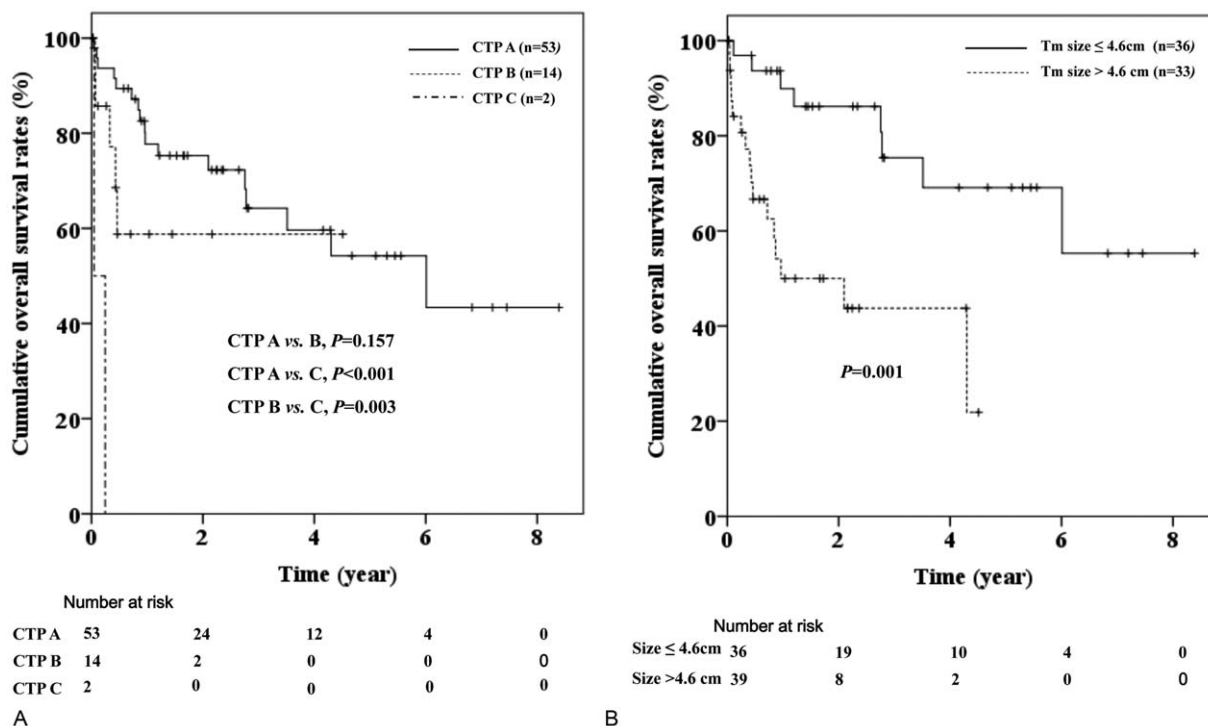


Figure 3. Cumulative overall survivals by CTP class and median tumor size in ALD-associated HCC patients without liver cirrhosis. The cumulative OS rates of patients with CTP class C were significantly lower than those of patients with CTP class A ($P < .001$) or class B ($P = .003$) (A), but no significant difference was observed between CTP class A and B patients ($P = .157$) (A). The cumulative OS rates of patients with a tumor size of ≤ 4.6 cm were significantly higher than those of patients with a tumor size of > 4.6 cm ($P < .007$) (B). ALD = alcoholic liver disease, CTP = Child-Turcotte-Pugh, HCC = hepatocellular carcinoma, OS = overall survival.

depending on geographic location and the cause of liver disease.^[5,24] Unlike HCC in cirrhotic livers, which is caused by stepwise carcinogenesis leading from regenerative nodules through dysplastic nodules to HCC, it has been reported that HCCs in non-cirrhotic liver arise due to de novo carcinogenesis.^[25–27] Moreover, various congenital and acquired factors,

such as, altered cell-cycle regulation, oxidative stress, tumorigenic growth factors, and genetic susceptibility have been reported to be associated with the development of HCC in non-cirrhotic livers.^[25–27] Alcohol intake may be related to HCC development with the mechanisms of direct (genotoxic) or indirect effects (cirrhosis development).^[28] Direct carcinogenic effect of alcohol

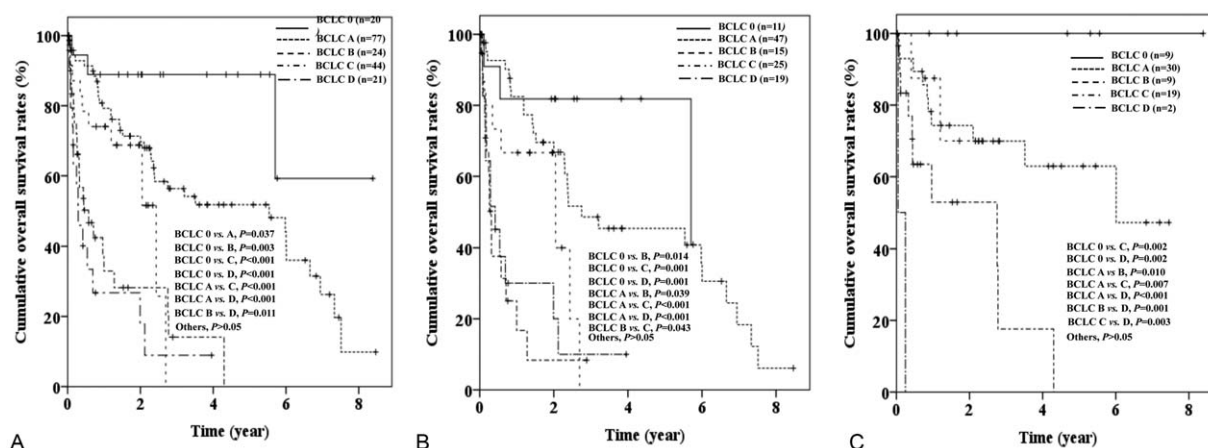


Figure 4. Cumulative overall survivals by BCLC stages in ALD-associated HCC patients of the 186 study subjects, the cumulative OS rates of patients with BCLC stage 0 were significantly greater than those of patients with BCLC stage A ($P = .037$), B ($P = .003$), C ($P < .001$), or D ($P < .001$) (A). In ALD-associated HCC patients with LC, the cumulative OS rates of patients with BCLC stage 0 were significantly greater than those of patients with BCLC stage B ($P = .014$), C ($P = .001$), or D ($P = .001$) (B). In ALD-associated HCC patients without LC, the cumulative OS rates of patients with BCLC stage 0 were significantly greater than those of BCLC stage C ($P = .002$) or ($P = .002$) patients (C). BCLC = Barcelona Clinic Liver Cancer, ALD = alcoholic liver disease, HCC = hepatocellular carcinoma, OS = overall survival, LC = liver cirrhosis.

Table 2
Significant predictive factors of overall survival of ALD-associated HCC patients with LC (n = 117).

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age (year)	1.01 (0.98–1.03)	.953	–	–
Gender (male)	1.18 (0.29–4.88)	.817	–	–
BMI (kg/m ²)	0.94 (0.87–1.01)	.087	–	–
DM, presence	1.39 (0.86–2.27)	.183	–	–
HTN, presence	1.09 (0.65–1.83)	.757	–	–
ALT (IU/L)	1.01 (0.99–1.01)	.09	–	–
CTP class				
A (reference)				
B	3.68 (2.07–6.55)	<.001	3.55 (1.91–6.57)	<.001
C	5.54 (2.66–11.55)	<.001	5.67 (2.62–12.25)	<.001
Tumor size (cm)	1.09 (1.02–1.16)	.008	1.11 (1.03–1.19)	.006
Tumor type				
diffuse vs nodular	5.72 (1.31–24.92)	.020	1.54 (0.31–7.72)	.597
AFP (ng/mL)	1.00 (1.00–1.01)	.032	1.00 (1.00–1.01)	.289
Treatment				
curative vs non-curative	0.33 (0.16–0.69)	.004	0.45 (0.20–0.99)	.048

AFP = Alpha-fetoprotein, ALD = alcoholic liver disease, ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, CTP = Child-Turcotte-Pugh classification, curative treatment: operation or radiofrequency ablation, DM = diabetes mellitus, HCC = hepatocellular carcinoma, HR = hazard ratio, HTN = hypertension, LC = liver cirrhosis. Event: death (n = 67).

may play a pivotal role in de novo carcinogenesis of non-cirrhotic HCC,^[25,29] which suggest non-cirrhotic HCC can clearly occur in ALD patients. Therefore, it is necessary to elucidate the clinical features, OS, or prognosis in ALD patients without LC.

The incidence of HCC arising in livers without cirrhosis, other than in cases of viral hepatitis, has not been accurately determined. Recently, it was reported that half of HCC patients with ALD had a non-cirrhotic liver, and that 19.2% and 32.5% of HCC patients with HBV or HCV, respectively, had non-cirrhotic livers.^[17] However, this previous study was limited by a small cohort (n = 44) of ALD-associated HCC patients, and the OSs of these patients were not evaluated. However, in this study, it is notable that a relatively large number (n = 186) of ALD-associated HCC patients was analyzed, and of these, about 37% did not have LC. We also analyzed the OS of ALD-associated

HCC according to the presence of LC, and compared OSs with respect to CTP class, tumor size, BCLC stage, and curative-intent treatment in those with or without LC. In addition, we sought to identify prognostic factors for OS in those with or without LC. Therefore, we believe that our results may be more useful for the management of ALD patients without LC than the previous study as regards HCC surveillance.^[17]

In terms of the OSs of HCC patients without LC, some previous studies analyzed the survival outcomes of patients with or without LC that received surgical resection or transplantation, and reported that OSs were better in those without LC.^[13,24] However, these studies did not also separately analyze the OSs of ALD-associated HCC patients with or without LC, and enrolled only small number of ALD patients. In another study,^[17] median OS was reported to be not different between HCC patients with

Table 3
Significant predictive factors of overall survival of ALD-associated HCC patients without LC (n = 69).

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Age (year)	1.02 (0.97–1.06)	.479	–	–
Gender (male)	1.38 (0.19–10.35)	.751	–	–
BMI (kg/m ²)	1.00 (0.89–1.14)	.948	–	–
DM, presence	0.56 (0.23–1.38)	.208	–	–
HTN, presence	0.91 (0.37–2.23)	.840	–	–
ALT (IU/L)	1.01 (0.99–1.01)	.129	–	–
CTP class				
A (reference)				
B	2.08 (0.74–5.81)	.164	1.42 (0.48–4.19)	.526
C	23.45 (4.29–127.97)	<.001	16.42 (2.91–92.62)	.002
Tumor size (cm)	1.09 (1.02–1.16)	.008	1.11 (1.02–1.22)	.023
AFP (ng/mL)	1.00 (1.00–1.01)	.065	–	–
Treatment				
curative vs non-curative	0.47 (0.18–1.28)	0.141		

AFP = Alpha-fetoprotein, ALD = alcoholic liver disease, ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, CTP = Child-Turcotte-Pugh classification, DM = diabetes mellitus, HCC = hepatocellular carcinoma, HR = hazard ratio, HTN = hypertension, LC = liver cirrhosis. Event: death (n = 24).

and without LC after liver resection or transplantation. Moreover, it was found that the majority of ALD patients had good reserve liver function (CTP class A), that is, 90.9% and 95.5% of those with and without LC, respectively. On the other hand, in the present study, OS was found to be better in those without LC than in those with LC, which suggest that a cirrhotic background liver impacts survival. In particular, given that moderate or poor reserve liver function of CTP class B or C was more frequently present in those with LC, it is possible that curative treatment was more frequently contraindicated in those with LC, and that this was responsible for the poorer prognosis observed in patients with LC. In fact, in the present study, curative-intent therapy was less frequently applied in patients with LC. However, this different treatment type between HCC patients with and without LC may be a confounding factor for OSs of all patients. Thus, we performed multivariable analysis for enrolled all 186 patients (supplementary Table 1, <http://links.lww.com/MD/D366>), and found that LC and treatment type (curative-intent treatment or not) were independent predictors for HCC patients' survival without affecting each other.

However, we failed to find a significant difference between the OSs of ALD-associated HCC patients with or without LC in subgroup analysis for those treated with curative-intent therapy, which concurs with that observed in the previous study.^[17] Moreover, in ALD-associated HCC patients without LC, OS was not different between patients received curative-intent therapy or not, unlike in those with LC. This may suggest that curative-intent treatment is more important for ALD-associated HCC patients prognosis than LC itself, or may be resulted by the small number of patients who received curative-intent therapy. For patients with non-curative treatment, we additionally analyzed OSs according to the presence of LC (supplementary Fig. 2A, <http://links.lww.com/MD/D365>), and found that the cumulative OSs of ALD-associated HCC patients without cirrhosis were significantly better than those with cirrhosis. This may suggest that the presence of LC itself is an important prognostic factor in ALD-associated HCC patient with non-curative treatment, unlike those with curative-intent treatment.

In this study, we found that ALD-patients without LC showed better liver function than those with LC. Interestingly, OS in those without LC was not significantly different between those with CTP classes A and B, although OS in those with LC followed CTP class order (A > B > C). Given that serum levels of bilirubin or PT are correctable in individuals with normal liver function, this may have been because serum levels of albumin, bilirubin, and PT were more correctable before treatment of HCC or during follow-up after treatment of HCC in patients with non-cirrhotic background liver, even with CTP class B. This explanation is also supported by our prognostic analysis, that is, CTP class B and C were found to be the worse prognostic factors of poorer OS in those with LC, whereas only CTP class C was a poor prognostic factor in those without LC. These results suggest that efforts should be made to calibrate CTP components aggressively in ALD-associated HCC patients without LC to improve their prognosis. In order to evaluate the prognostic impact of LC or not according to CTP classification, we additionally analyzed survival outcome in all study patients, and the results are showed in supplementary Fig. 2B, <http://links.lww.com/MD/D365>, C, <http://links.lww.com/MD/D365>, and D, <http://links.lww.com/MD/D365>. In each CTP class, the cumulative OSs were not significantly different between patients with and without LC. These findings may suggest that LC itself did not significantly

affect the survival rates of patients in the same CTP class, and that liver function rather the presence of cirrhosis itself predicts prognosis of alcohol-related HCC patients.

Although tumor size alone in HCC is not an absolute contraindication to curative-intent treatment, such as, surgical resection or transplantation,^[10] it does serve as a surrogate marker of the presence of microvascular invasion, which is an important predictor of prognosis in HCC patients.^[30-32] Our multivariate analysis results showed tumor size importantly predicted prognosis of HCC patients with and without LC, respectively. However, in this study, there are 2 interesting results. First, the tumor size was significantly larger in HCC patients without LC compared to those with LC, and HCC patients with larger tumor size showed poor prognosis than those with smaller tumor size. If we look at these 2 results, HCC patients without LC may show poor prognosis, but in this study, HCC patients without LC showed better OSs than those with LC. In order to identify the independent prognostic values of tumor size regardless of the presence of LC, we additionally performed multivariable analysis for enrolled all 186 patients (supplementary Table 1, <http://links.lww.com/MD/D366>), and found that tumor size and LC were independent predictors for HCC patients' survival without affecting each other. Furthermore, greater tumor size in ALD-associated HCC without LC suggests that they had not been under surveillance for HCC. Interestingly, single HCC tended to be more frequently found in ALD-associated HCC patients without LC than in those with LC. Therefore, the frequency of very early or early staged HCC (BCLC stage 0 or A) tended to be higher in those without LC than in those with LC. This suggests curative-intent treatment can be more likely to be applied to those without LC, resulting in better OS in these patients despite the presence of larger tumor size, a poorer prognostic factor for HCC. These results indicated that if ALD patients without LC are more closely and systemically monitored for HCC, the disease would be detected earlier and prognoses would be improved. Thus, we suggest that studies be conducted on the cost-effectiveness of HCC surveillance in this patient population.

This study has several limitations. First, it is inherently limited by selection bias due to its retrospective design. Second, LC was not histologically diagnosed, but, in real-life clinical setting, liver biopsy was not mandatory. Finally, the absolute number of ALD-associated HCC patients without LC in this study was only 69, and this prevented out being able to demonstrate the effects of treatment with curative-intent on survival outcomes in these patients. However, given that the incidence of HCC in patients without LC is not accurately known, especially in ALD patients, we believe that our results provide useful information for management for these patients.

In conclusions, this retrospective study shows that OS of ALD-associated HCC patients without LC was better than in those with LC. Moreover, OS was comparable between patients with CTP class A and B in ALD-associated HCC patients without LC. Interestingly, tumor size was greater in ALD-associated HCC patients without LC than in those with LC, and about 43% of ALD-associated HCC patients without LC had intermediate or advanced staged HCC. These findings suggest that ALD-associated HCC patients without LC had not been enrolled in any surveillance program for HCC. Given that ALD-associated HCC patients without LC can suffer from HCC, it is necessary to establish new management strategies for them, especially to discourage excessive drinking. Moreover, we suggest that

well-designed prospective randomized controlled trials be undertaken to confirm our results.

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