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Editorial board member of *World Journal of Gastroenterology*, Alexander Link, MD, PhD, Academic Research, Associate Professor, Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital Magdeburg, Magdeburg 39120, Germany

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Retrospective Cohort Study

Correlation between smoking habit and surgical outcomes on viral-associated hepatocellular carcinomas

Keita Kai, Sho Komukai, Hiroki Koga, Koutaro Yamaji, Takao Ide, Atsushi Kawaguchi, Shinichi Aishima, Hirokazu Noshiro

Keita Kai, Shinichi Aishima, Department of Pathology, Saga University Hospital, Saga 849-8501, Japan

Sho Komukai, Clinical Research Center, Saga University Hospital, Saga 849-8501, Japan

Hiroki Koga, Koutaro Yamaji, Takao Ide, Hirokazu Noshiro, Department of Surgery, Saga University Faculty of Medicine, Saga 849-8501, Japan

Atsushi Kawaguchi, Center for Comprehensive Community Medicine, Saga University Faculty of Medicine, Saga 849-8501, Japan

Koutaro Yamaji, Shinichi Aishima, Department of Pathology and Microbiology, Saga University Faculty of Medicine, Saga 849-8501, Japan

ORCID number: Keita Kai (0000-0003-1553-2598); Sho Komukai (0000-0002-4329-2520); Hiroki Koga (0000-0003-2529-0529); Koutaro Yamaji (0000-0001-8801-4068); Takao Ide (0000-0003-2441-4438); Atsushi Kawaguchi (0000-0002-8911-3321); Shinichi Aishima (0000-0002-1448-6510), Hirokazu Noshiro (0000-0003-3227-7816).

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Correspondence to: Keita Kai, MD, PhD, Department of Pathology, Saga University Hospital, Nabeshima 5-1-1, Saga City, Saga 849-8501, Japan. kaikeit@cc.saga-u.ac.jp
Telephone: +81-952-343264
Fax: +81-952-342055

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Abstract**AIM**

To investigate the association between smoking habits and surgical outcomes in hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) (B-HCC) and hepatitis C virus (HCV)-related HCC (C-HCC) and clarify the clinicopathological features associated with smoking status in B-HCC and C-HCC patients.

METHODS

We retrospectively examined the cases of the 341 consecutive patients with viral-associated HCC (C-HCC, $n = 273$; B-HCC, $n = 68$) who underwent curative surgery for their primary lesion. We categorized smoking status at the time of surgery into never, ex- and current smoker. We analyzed the B-HCC and C-HCC groups' clinicopathological features and surgical outcomes, *i.e.*, disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS). Univariate and multivariate analyses were performed using a Cox proportional hazards regression model. We also performed subset analyses in both patient groups comparing the current smokers to the other patients.

RESULTS

The multivariate analysis in the C-HCC group revealed that current-smoker status was significantly correlated with both OS ($P = 0.0039$) and DSS ($P = 0.0416$). In the B-HCC patients, no significant correlation was observed between current-smoker status and DFS, OS, or DSS in the univariate or multivariate analyses. The subset analyses comparing the current smokers to the other patients in both the C-HCC and B-HCC groups revealed that the current smokers developed HCC at significantly younger ages than the other patients irrespective of viral infection status.

CONCLUSION

A smoking habit is significantly correlated with the overall and disease-specific survivals of patients with C-HCC. In contrast, the B-HCC patients showed a weak association between smoking status and surgical outcomes.

Key words: Hepatocellular carcinoma; Hepatitis B virus; Hepatitis C virus; Smoking; Surgery; Prognosis

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Core tip: We retrospectively analyzed the association between smoking habits and surgical outcomes in 68 cases of hepatitis B virus-related hepatocellular carcinoma (HCC) (B-HCC) and 273 cases of hepatitis C virus (HCV)-related HCC (C-HCC). Smoking habit was revealed as significantly correlated with the overall survival and disease-specific survival of the C-HCC patients, whereas the B-HCC patient group showed a weak association between smoking habit and surgical outcomes. Our subset analyses comparing the current smokers to the other patients revealed that the current smokers developed HCC at significantly younger ages compared to the other patients irrespective of viral infection status.

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INTRODUCTION

Hepatocellular carcinoma (HCC), is the fifth most common cancer in the world and the second most common cause of cancer deaths, accounting for about 745000 deaths per year globally^[1]. Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections represent the leading cause of HCC (60%-70%), with a total incidence of 16/100000 globally^[2]. The prevalence of HBV and HCV infections varies among geographic regions. In Japan, HCV-related HCC (C-HCC) is the most common HCC infection, accounting for approx. 70% of all HCC cases^[3].

It is reported that the natural histories of C-HCC and HBV-related HCC (B-HCC) differ: HCV infection leads to the development of HCC mainly through indirect pathways (such as chronic inflammation, cell deaths and proliferation) whereas HBV causes HCC through direct and indirect pathways as it can integrate into the host genome, affecting cellular signaling and growth control^[4]. HCC is thus typically found in HCV patients with cirrhosis, although it is sometimes found in HBV patients without significant liver cirrhosis.

Curative surgical resection is the most frequent therapeutic strategy for HCC. The influence of the patients' viral infection status on surgical outcomes has been well investigated. A meta-analysis in 2011 reported that non-B non-C (NBNC)-HCC patients showed significantly better disease-free survival (DFS) surgical outcomes; in addition, although the result was not statistically significant, the overall survival (OS) of NBNC-HCC patients was more favorable compared to that of both B-HCC and C-HCC patients^[5]. This meta-analysis of 20 studies also reported that the OS and the DFS were not significantly different between B-HCC and C-HCC groups^[5]. A Japanese nationwide study of nearly 12000 patients also reported that both the OS and DFS after surgical resection were not significantly different between the C-HCC and B-HCC groups, although the liver function in the C-HCC group was significantly worse than that in the B-HCC group^[6].

Generally, lifestyle-associated factors such as metabolic disease, alcohol consumption, and smoking status have tended to be left out of investigations when discussing factors affecting the pathogenesis or surgical outcomes of viral-associated HCC. It is well known that lifestyle factors are significantly involved in the carcinogenesis of NBNC-HCC and it has been reported that metabolic factors correlate also with prognosis of NBNC-HCC^[7]. Although epidemiological studies obtained evidence that smoking habit is involved in HCC carcinogenesis^[8-10], little attention has

been paid to the relationship between smoking habit and surgical outcomes of HCC.

We recently analyzed the relationship between smoking status and surgical outcomes in patients with NBNC-HCC, and our analysis revealed that smoking habits are significantly correlated with the curatively resected surgical outcomes of NBNC-HCC^[11]. We then speculated that if smoking habits truly affect the postoperative prognosis of NBNC-HCC by one or more unknown mechanisms, smoking habits might also affect the postoperative prognosis of viral-associated HCC patients. In addition, since the natural histories of NBNC-HCC, B-HCC, and C-HCC differ, the clinicopathologic characteristics associated with smoking status might be different per viral infection status.

We thus conducted the present study to (1) investigate the association between smoking habits and surgical outcomes in B-HCC and C-HCC patients who underwent curative surgery; and (2) clarify the clinicopathological features associated with smoking habits in patients with B-HCC or C-HCC.

MATERIALS AND METHODS

The patient series and our definition of smoking status

This retrospective study's protocol was reviewed by the Ethics Committee of the Faculty of Medicine at Saga University and approved (approval No. 28-23). The written informed consent for the use of their clinical information was obtained from all of the study's patients. From 1984 to 2012, consecutive 477 cases of curative surgery for primary HCC at Saga University Hospital (in the city of Saga, which is located on the island of Kyushu, the southwestern-most of Japan's main islands) were initially enrolled the study. Definition of the HBV infection and HCV infection was HBsAg-positive and HCVAb-positive in serological tests, respectively. We excluded the following patients: those with NBNC-HCC (serologically both HBsAg- and HCVAb-negative) cases ($n = 83$) and those with co-infection of HBV with HCV ($n = 9$). Among the remaining 385 cases of C-HCC or B-HCC, we included only the cases for which all of the following information was available: the patient's age, gender, body mass index (BMI), diabetes mellitus status, smoking status (as defined below), alcohol abuse status, tumor size, status of portal vein invasion (Vp), number of primary tumors (solitary or multiple), T factor of the TMN classification, indocyanine green retention rate at 15 minutes (ICG R15), and serum alpha-fetoprotein (AFP) level. The final patient series was comprised of the 341 patients with viral-associated HCC (C-HCC, $n = 273$; B-HCC, $n = 68$).

We obtained the information about smoking status and alcohol abuse status from the patients' medical records. This information had been self-reported by the patients in an interview by medical staff. Each patient's smoking status at the time of surgery was categorized into never smoker, ex-smoker, and current smoker

based on the definitions in our recent study^[11], as follows. 'Never smoker' is self-explanatory. 'Ex-smoker' was defined as having quit smoking completely ≥ 1 year before the patient's surgery. Definition of 'Current smoker' was an individual who continued to smoke within 1 year prior to the surgery.

We have defined alcohol abuse as a daily ethanol intake > 40 g for men and > 20 g for women.

Statistical analyses

Statistical analyses were performed by the authors Komukai S and Kawaguchi A, who are statisticians. The software JMP ver. 12.2 and SAS ver. 9.4 (SAS, Cary, NC, United States) were used for the statistical analyses. They compared pairs of groups by Fisher's exact test, the χ^2 test and Student's *t*-test, as appropriate. The patients' DFS, OS and disease-specific survival (DSS) were determined as described^[11]. A univariate analysis and a multivariate analysis were performed using a Cox proportional hazards regression model.

The multivariate analysis was conducted in order to adjust the potential covariates in the comparison of smoking status groups; the patients' age and gender were always kept in the model, and other parameters were identified by the stepwise procedure using the *P* value threshold of 0.2. The complete patient series' median age (67 years old) was used as the age cut-off. The Kaplan-Meier method was used for calculating each of the postoperative survival curves. The log-rank test was used to compare the differences in survival curves. *P* value < 0.05 were accepted as significant.

RESULTS

Comparison of clinicopathological features and surgical outcomes between the HBV-related HCC and HCV-related HCC patients

The clinicopathological features of 273 cases of C-HCC and 68 cases of B-HCC are summarized in Table 1. The B-HCC group developed HCC at significantly younger ages (mean 57.15 years old) compared to the C-HCC group (mean: 67.16 years, $P < 0.0001$). Both the C- and B-HCC groups showed a male predominance, and the B-HCC patients showed a higher male predominance rate (86.76%) compared to the C-HCC patients (74.36%, $P = 0.03$).

Regarding smoking status, no significant difference was observed between the two groups although the B-HCC group tended to have more current smokers (47.06%) compared to the C-HCC group (32.23%). The status of alcohol abuse, diabetes mellitus, and BMI did not differ between the C- and B-HCC patients.

The percentage of ICG R15 was significantly higher in the C-HCC group compared to the B-HCC group ($P < 0.0001$), indicating that the patients with HCV infection developed HCC at a more advanced stage of chronic hepatitis compared to the patients with HBV infection. The serum AFP level of at the time of surgery tended to be higher in the B-HCC patients compared to the

Table 1 Clinicopathologic features of the hepatitis C virus-hepatocellular carcinoma and hepatitis B virus-hepatocellular carcinoma *n* (%)

	HCV (<i>n</i> = 273)	HBV (<i>n</i> = 68)	<i>P</i> value
Age (mean ± SD)	67.16 ± 8.56	57.15 ± 12.47	< 0.0001
Gender			
Male	203 (74.36)	59 (86.76)	0.0300
Female	70 (25.64)	9 (13.24)	
Smoking habit			
Never	111 (40.66)	21 (30.88)	0.0715
Ex	74 (27.11)	15 (22.06)	
Current	88 (32.23)	32 (47.06)	
Alcohol abuse			
(+)	63 (23.08)	22 (32.35)	0.1136
(-)	210 (76.92)	46 (67.65)	
Diabetes mellitus			
(+)	62 (22.71)	12 (17.65)	0.3647
(-)	211 (77.29)	56 (82.35)	
BMI (mean ± SD)	22.49 ± 3.29	22.93 ± 3.80	0.3478
ICG R15 (%) (mean ± SD)	18.63 ± 9.03	13.31 ± 6.30	< 0.0001
AFP (ng/mL), Median (range)	26.2 (0, 29800)	31 (1, 271600)	0.0625
Tumor size (mean ± SD mm)	37.37 ± 25.62	49.72 ± 33.14	0.0052
Solitary/Multiple			
Solitary	182 (66.67)	41 (60.29)	0.3230
Multiple	91 (33.33)	27 (39.71)	
Vp			
(+)	74 (27.11)	29 (42.65)	0.0125
(-)	199 (72.89)	39 (57.35)	
T factor			
T1/2	156 (57.14)	32 (47.06)	0.1347
T3/4	117 (42.86)	36 (52.94)	

HCV: Hepatitis C virus; HBV: Hepatitis B virus.

C-HCC patients, but the difference was not significant. The tumor sizes in the B-HCC group were significantly larger than those of the C-HCC group (mean tumor sizes 49.72 mm vs 37.37 mm, $P = 0.0052$), and the percentage of Vp was significantly higher in the B-HCC group compared to the C-HCC (42.65% vs 27.11%, $P = 0.0125$). There was no significant difference regarding T factor or multiple occurrence between the B- and C-HCC groups.

We compared the surgical outcomes (DFS, OS, DSS) of the B-HCC and C-HCC groups and found no significant difference between the groups in DFS, OS or DSS (Figure 1).

Univariate analysis results and survival curves per smoking status in the HCV-related HCC patients

The results of the univariate analyses for surgical outcomes in the C-HCC patient group are summarized in Table 2. The factors that were significantly correlated with the DFS of the C-HCC patient group were alcohol abuse ($P = 0.0321$), BMI ($P = 0.0270$), ICG R15 ($P = 0.0088$), tumor size ($P = 0.0305$), multiple tumors ($P = 0.0021$), and T factor ($P < 0.0001$). Smoking status was not correlated with the DFS of the C-HCC patients.

The factors that were revealed to be significantly correlated with the OS of the C-HCC patient group were smoking (current vs other; $P = 0.0144$), serum AFP level ($P = 0.0402$), tumor size ($P = 0.0019$), multiple tumors ($P = 0.0001$), Vp ($P = 0.0004$), and T factor ($P = 0.0008$).

The factors found to be significantly correlated with disease-specific survival were smoking (current vs other; $P = 0.0483$), tumor size ($P = 0.0070$), Vp ($P = 0.0177$), and T factor ($P = 0.0315$). The survival curves per smoking habit are demonstrated in Figure 2A-C. The current-smoking group showed significantly poor survival curves compared to the never + Ex patient group for both OS and DSS. However, no significant difference was observed in DFS between the current-smoking group and never + Ex patient group.

Multivariate analysis results per smoking status in HCV-related HCC patients

The results of the multivariate analyses for DFS, OS and DSS are summarized in Table 3. Current-smoker status showed no correlation with DFS ($P = 0.2364$). The factors that were significantly correlated with DFS were alcohol abuse ($P = 0.0025$), BMI ($P = 0.0165$), ICG R15 ($P = 0.0027$) and T factor ($P < 0.0001$). In the multivariate analysis for OS, current-smoker status was significantly correlated with OS ($P = 0.0039$). The only other factor that was significantly correlated with OS was T factor ($P = 0.0005$). The factors significantly correlated with DSS were current-smoker status and T factor ($P = 0.0416$ and $P = 0.0226$, respectively).

Univariate analysis results and survival curves for the HBV-related HCC patients per smoker status

The results of the univariate analyses for surgical outcomes in the B-HCC group are summarized in Table

Table 2 Univariate analysis results: Disease-free, overall and disease-specific survival after hepatic resection for hepatocellular carcinoma (hepatitis C virus, $n = 273$)

Characteristics	<i>n</i>	DFS		OS		DSS	
		HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
Age			0.9234		0.5143		0.7101
≤ 67	133	1		1		1	
> 67	140	1.01381 (0.7665, 1.3409)		1.10679 (0.8159, 1.5015)		0.92155 (0.599, 1.4177)	
Gender			0.5699		0.5110		0.2434
Female	70	1		1		1	
Male	203	0.91269 (0.666, 1.2508)		1.12916 (0.786, 1.6221)		1.38366 (0.8019, 2.3876)	
Smoking habit (Ex + current)			0.5978		0.1262		0.2147
Absent	111	1		1		1	
Present	162	0.92696 (0.6994, 1.2286)		1.27849 (0.9332, 1.7516)		1.32797 (0.8483, 2.0788)	
Smoking habit (current)			0.8864		0.0144		0.0483
Absent	185	1		1		1	
Present	88	1.02258 (0.7527, 1.3892)		1.47783 (1.0808, 2.0207)		1.55795 (1.0033, 2.4192)	
Alcohol abuse			0.0321		0.8232		0.7027
Absent	210	1		1		1	
Present	63	0.68132 (0.4797, 0.9678)		0.95952 (0.6677, 1.3788)		0.90325 (0.5356, 1.5232)	
Diabetes mellitus			0.3149		0.5259		0.9487
Absent	211	1		1		1	
Present	62	1.18657 (0.85, 1.6564)		1.12207 (0.7861, 1.6017)		0.98302 (0.5831, 1.6572)	
BMI			0.0270		0.2082		0.6409
≤ Median	137	1		1		1	
> Median	136	0.72863 (0.5503, 0.9647)		0.82193 (0.6056, 1.1155)		0.9026 (0.5868, 1.3884)	
ICG R15 (%)			0.0088		0.2391		0.6896
≤ Median	111	1		1		1	
> Median	162	1.47199 (1.1021, 1.9659)		1.20672 (0.8825, 1.65)		1.09334 (0.7056, 1.6941)	
AFP			0.2274		0.0402		0.1371
≤ Median	136	1		1		1	
> Median	137	1.18795 (0.8981, 1.5713)		1.37689 (1.0144, 1.8689)		1.38776 (0.901, 2.1376)	
Tumor size			0.0305		0.0019		0.0070
≤ Median	161	1		1		1	
> Median	112	1.37235 (1.0303, 1.828)		1.63014 (1.1982, 2.2178)		1.81608 (1.1773, 2.8016)	
Solitary/Multiple			0.0021		0.0001		0.1182
Solitary	182	1		1		1	
Multiple	91	1.59365 (1.1835, 2.1459)		1.8536 (1.3563, 2.5332)		1.43932 (0.9115, 2.2728)	
Vp			0.0767		0.0004		0.0177
Absent	199	1		1		1	
Present	74	1.33528 (0.9695, 1.839)		1.81728 (1.3073, 2.5262)		1.76737 (1.104, 2.8294)	
T12/T34			< 0.0001		0.0008		0.0315
T12	156	1		1		1	
T34	117	1.81021 (1.3644, 2.4017)		1.68381 (1.2412, 2.2843)		1.60589 (1.0429, 2.4728)	

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.

4. The factors that were significantly correlated with the DFS of the B-HCC patient group were alcohol abuse ($P = 0.0183$), multiple tumors ($P = 0.0002$) and T factor ($P = 0.0042$). The factors significantly correlated with the OS of the B-HCC group were the serum AFP level ($P = 0.0015$), multiple tumors ($P = 0.0001$), Vp ($P = 0.0035$), and T factor ($P = 0.0001$). The factors revealed to be significantly correlated with disease-specific survival were the serum AFP level ($P = 0.0114$), multiple tumors ($P = 0.0013$), Vp ($P = 0.0362$), and T factor ($P = 0.0019$).

The survival curves of DFS, OS and DSS per smoking status are demonstrated in Figure 2D-F. Smoking status was not correlated with the DFS, OS or DSS of the B-HCC patients.

Multivariate analysis results regarding smoking status in the HBV-related HCC patients

The results of the multivariate analyses are summarized

in Table 5. The two factors that were significantly correlated with the DFS of the B-HCC patients were alcohol abuse ($P = 0.0119$) and multiple tumors ($P = 0.0004$). The factors that were significantly correlated with the patients' OS were alcohol abuse ($P = 0.0312$) and multiple tumors ($P = 0.0001$). The only factor that was significantly correlated with disease-specific survival was multiple tumors ($P = 0.0009$). Current-smoker status showed no correlation with any DFS, OS or DSS.

Comparison of clinicopathological factors per current-smoker status in the HCV-related HCC and HBV-related HCC groups

To clarify the clinicopathological characteristics of the current smokers in the C-HCC and B-HCC groups, we performed subset analyses regarding the clinicopathological factors per current-smoker status (Table 6).

Among the C-HCC patients, the current smokers

Table 3 Multivariate analyses for current smokers *vs* others (hepatitis C virus, *n* = 273)

Type	Characteristics	HR (95%CI)	P value
DFS	Smoking habit (current)	1.22892 (0.8736, 1.7287)	0.2364
	Age (67 < yr)	0.98815 (0.7442, 1.3121)	0.9343
	Gender (male)	0.9536 (0.6797, 1.338)	0.7833
	Alcohol abuse	0.55622 (0.3803, 0.8135)	0.0025
	BMI (median <)	0.70403 (0.5284, 0.9381)	0.0165
	ICG R15 (median <)	1.59531 (1.1763, 2.1635)	0.0027
OS	T factor (T3/4)	1.90638 (1.4279, 2.5452)	< 0.0001
	Smoking habit (current)	1.69259 (1.1844, 2.4187)	0.0039
	Age (67 < yr)	1.18434 (0.8668, 1.6182)	0.2880
	Gender (male)	1.01654 (0.687, 1.504)	0.9346
	Alcohol abuse	0.74612 (0.5061, 1.1)	0.1392
	BMI (median <)	0.89005 (0.6489, 1.2208)	0.4701
DSS	ICG R15 (median <)	1.32015 (0.9524, 1.83)	0.0955
	T factor (T3/4)	1.74555 (1.2767, 2.3865)	0.0005
	Smoking habit (current)	1.68394 (1.0201, 2.7798)	0.0416
	Age (67 < yr)	1.00555 (0.6464, 1.5644)	0.9804
	Gender (male)	1.25081 (0.6981, 2.2412)	0.4520
	Alcohol abuse	0.66203 (0.3796, 1.1547)	0.1462
	BMI (median <)	0.97081 (0.6206, 1.5185)	0.8967
	ICG R15 (median <)	1.18278 (0.7484, 1.8692)	0.4722
	T factor (T3/4)	1.67615 (1.0752, 2.613)	0.0226

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.

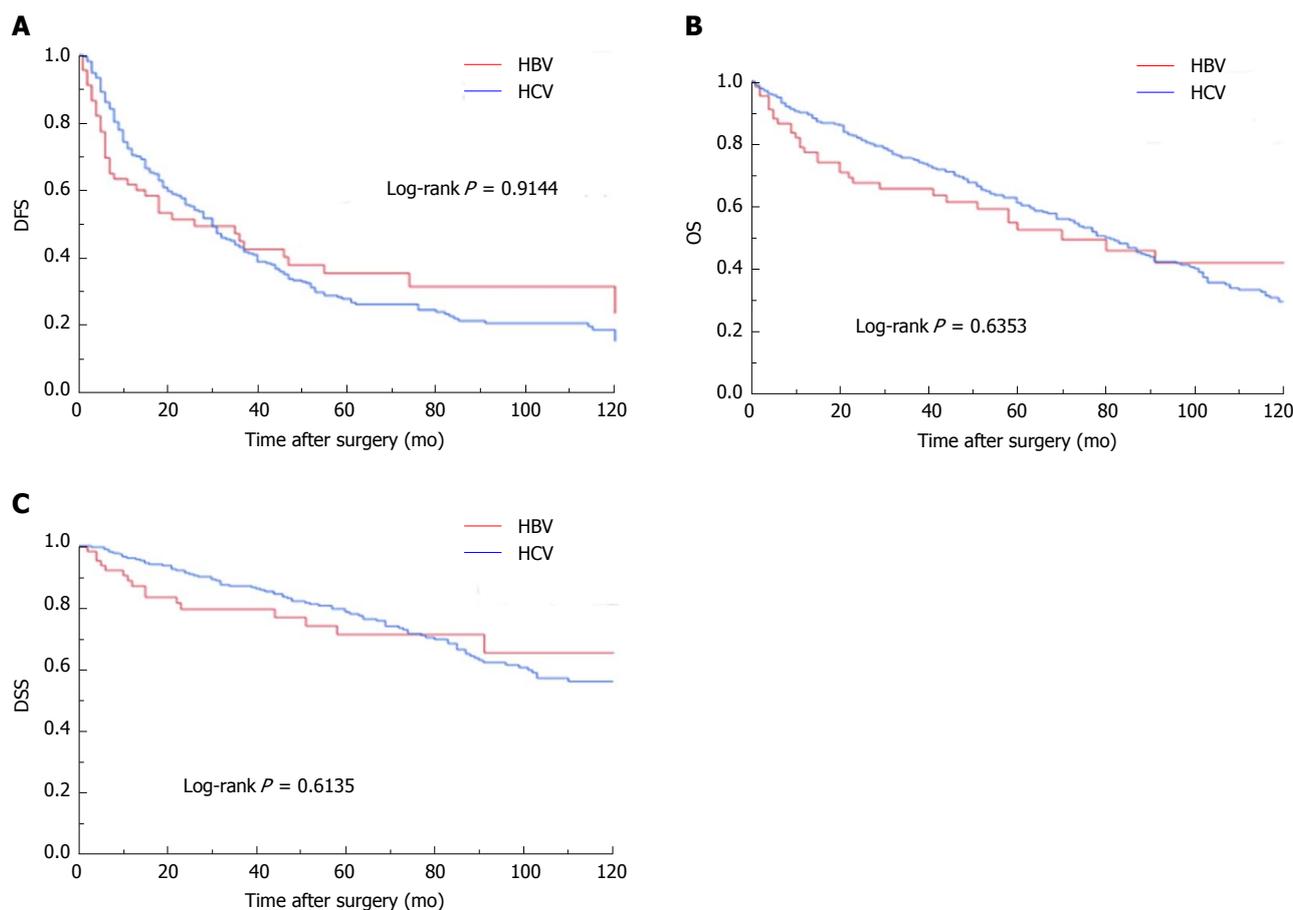


Figure 1 Kaplan-Meier curves according to viral infection status for disease-free survival (A), overall survival (B) and disease-specific survival (C). DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.

were slightly but significantly younger than the never + Ex patients (mean age 65.34 years vs 68.02 years, $P = 0.0153$) at the time of surgery. The current smokers showed significant male predominance (P

< 0.0001) and had a significantly greater incidences of alcohol abuse ($P < 0.0001$). The BMI and ICG R15 values of the current smokers were both significantly lower than those of the never+Ex patients ($P = 0.0031$

Table 4 Univariate analysis results: Disease-free, overall and disease-specific survival after hepatic resection for hepatocellular carcinoma (hepatitis B virus, *n* = 68)

Characteristics	<i>n</i>	DFS		OS		DSS	
		HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
Age			0.9417		0.8991		0.3769
≤ 67	54	1		1		1	
> 67	14	0.97131 (0.445, 2.1202)		1.05615 (0.4541, 2.4565)		0.5123 (0.1162, 2.2588)	
Gender			0.6063		0.1844		0.3363
Female	9	1		1		1	
Male	59	1.28118 (0.4993, 3.2876)		2.64152 (0.6294, 11.0865)		2.70202 (0.3562, 20.4981)	
Smoking habit (Ex + current)			0.8323		0.5660		0.9544
Absent	21	1		1		1	
Present	47	0.93056 (0.478, 1.8115)		1.26612 (0.5656, 2.8343)		0.96953 (0.336, 2.7975)	
Smoking habit (current)			0.4008		0.3620		0.8001
Absent	36	1		1		1	
Present	32	1.30547 (0.7009, 2.4314)		1.38988 (0.6848, 2.8209)		1.13501 (0.4258, 3.0251)	
Alcohol abuse			0.0183		0.0706		0.5674
Absent	46	1		1		1	
Present	22	0.4139 (0.199, 0.861)		0.45823 (0.1966, 1.0679)		0.73339 (0.2534, 2.1228)	
Diabetes mellitus			0.4682		0.6700		0.8752
Absent	56	1		1		1	
Present	12	1.32065 (0.6229, 2.7999)		1.21513 (0.4959, 2.9773)		1.10618 (0.3141, 3.8962)	
BMI			0.3087		0.9126		0.6383
≤ Median	33	1		1		1	
> Median	35	1.3863 (0.7392, 2.6)		0.96125 (0.4746, 1.9468)		1.26746 (0.4718, 3.4046)	
ICG R15 (%)			0.6240		0.8562		0.5468
≤ Median	49	1		1		1	
> Median	19	0.83516 (0.4064, 1.7163)		1.07744 (0.4808, 2.4147)		1.38526 (0.4799, 3.9983)	
AFP			0.0665		0.0015		0.0114
≤ Median	34	1		1		1	
> Median	34	1.80218 (0.9606, 3.3809)		3.54578 (1.6235, 7.7443)		4.36412 (1.3942, 13.6606)	
Tumor size			0.1252		0.2124		0.0585
≤ Median	28	1		1		1	
> Median	40	1.67393 (0.8665, 3.2339)		1.61822 (0.7594, 3.4483)		3.37156 (0.9574, 11.8735)	
Solitary/Multiple			0.0002		0.0001		0.0013
Solitary	41	1		1		1	
Multiple	27	3.30417 (1.7552, 6.2201)		4.6829 (2.1913, 10.0073)		6.42975 (2.0644, 20.0257)	
Vp			0.0598		0.0035		0.0362
Absent	39	1		1		1	
Present	29	1.85208 (0.975, 3.5182)		2.94188 (1.4258, 6.07)		2.92487 (1.0717, 7.9823)	
T12/T34			0.0042		0.0001		0.0019
T12	32	1		1		1	
T34	36	2.60213 (1.3531, 5.0043)		5.55785 (2.3542, 13.1211)		10.58522 (2.3795, 47.0876)	

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.

and 0.0005, respectively). No significant difference was observed in diabetes mellitus, serum AFP level, tumor size, multiple tumor, Vp, T factor, or recurrence between the current smokers and the other patients.

In the B-HCC patient group, although the current smokers were significantly younger (mean age 53.66 years vs 60.25 years, *P* = 0.0284) and showed a significant male predominance (*P* = 0.0204), no significant difference was observed in any of the other factors between the current smokers and the other patients.

DISCUSSION

There have been many studies regarding cigarette smoking and the risk of developing HCC, and a recent meta-analysis confirmed the relationship between smoking and an increased risk of HCC development and mortality from HCC^[12]. Including our previous study^[11], there have been only a few studies focusing on the

correlation between smoking status and the surgical outcomes of hepatectomy or liver transplantation for HCC^[12-15]. The present study is the first to compare C-HCC and B-HCC regarding smoking status and surgical outcomes.

The most salient finding of this study is that the correlations between smoking status and surgical outcomes were notably different between the B-HCC and C-HCC patient groups. Although the current-smoking habit affected the surgical outcomes of the C-HCC patients, no significant association was found between smoking status and surgical outcomes in the B-HCC patients. As the current-smoking habit was revealed as an independent prognostic factor for both the OS and disease-specific survival in our C-HCC group, the tumors that had developed in the current smokers were indicated to have more aggressive malignant potential than the tumors that developed in the never- and ex-smokers. The continued elucidation of the

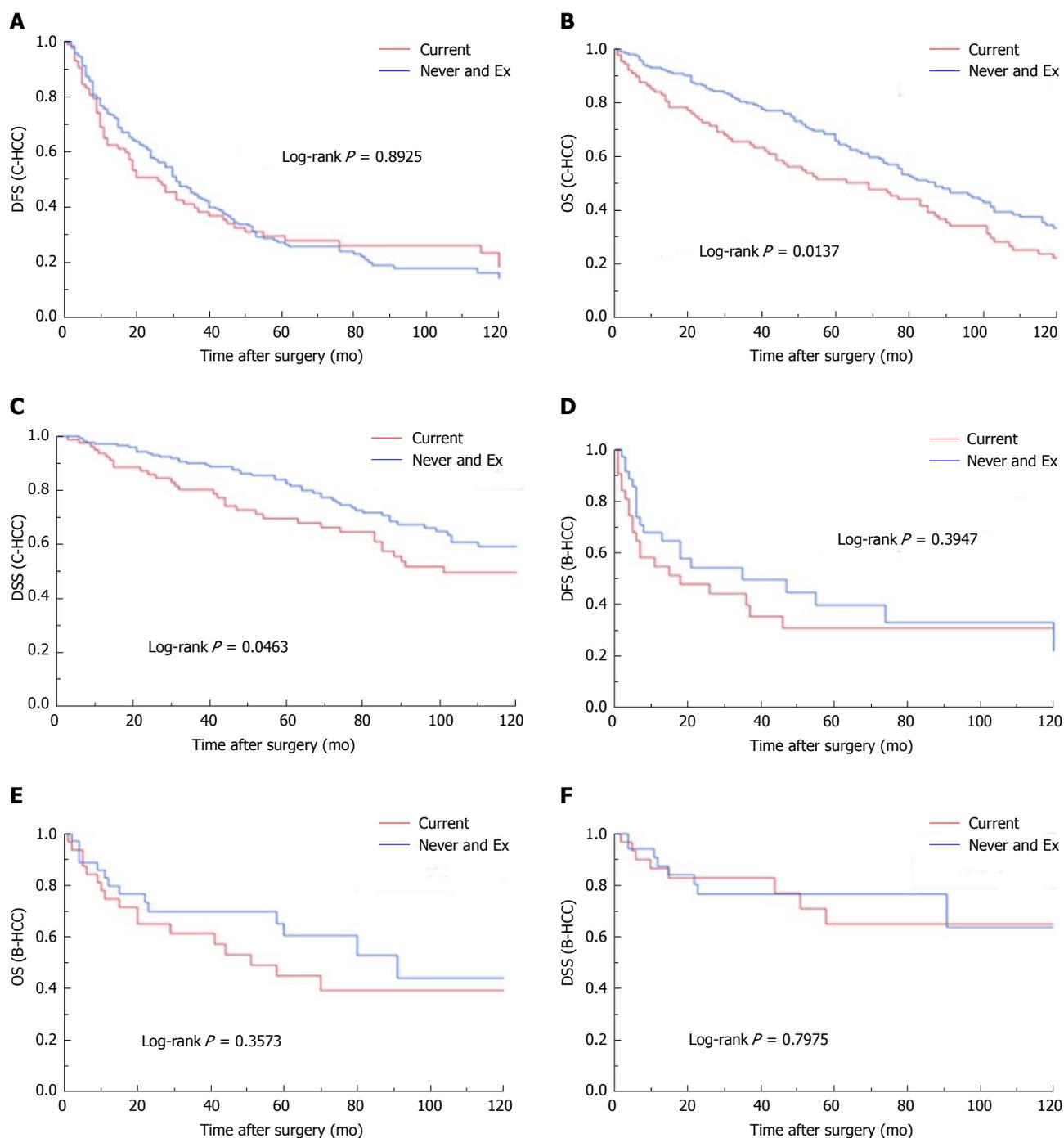


Figure 2 Kaplan-Meier curves according to smoking status for disease-free survival, overall survival and disease-specific survival in the hepatitis C virus-related hepatocellular carcinoma patients (A-C) and hepatitis B virus-related hepatocellular carcinoma patients (D-F).

pathological and molecular mechanisms underlying the development is a very important research focus, and we suspect that the difference in the natural histories of C-HCC and B-HCC is a key factor in the difference in the smoking status and surgical outcomes between B-HCC and C-HCC.

Generally, HCV-infected individuals develop HCC after long-term chronic hepatitis, and C-HCCs are typically found in patients with cirrhosis^[16]. Activated inflammatory cells release reactive oxygen species and induce lipid peroxidation, which promotes a pro-

oncogenic environment and DNA damage^[17] and increases DNA methylation^[18,19]. Thus, C-HCC develops mainly *via* an indirect pathway caused by chronic inflammation and an epigenetic process.

Although the mechanism of the carcinogenesis of HCC due to smoking has not been fully elucidated, it is reported that smoking yields chemicals with oncogenic potential such as hydrocarbons, nitrosamine, tar and vinyl chloride and a major source of 4-aminobiphenyl, a hepatic carcinogen which has been implicated as a causal risk factor for HCC^[20]. These oncogenic chemicals

Table 5 Multivariate analyses for current smokers vs others (hepatitis B virus, n = 68)

Type	Characteristics	HR (95%CI)	P value
DFS	Smoking habit (current)	1.41417 (0.7413, 2.698)	0.2930
	Age (67 < yr)	0.9339 (0.4189, 2.0818)	0.8672
	Gender (male)	1.82154 (0.6845, 4.8477)	0.2298
	Alcohol abuse	0.37957 (0.1785, 0.8072)	0.0119
	Multiple tumor	3.18518 (1.6783, 6.045)	0.0004
OS	Smoking habit (current)	1.43613 (0.6865, 3.0045)	0.3365
	Age (67 < yr)	0.88873 (0.3727, 2.119)	0.7902
	Gender (male)	3.66949 (0.8392, 16.0457)	0.0842
	Alcohol abuse	0.38587 (0.1622, 0.9177)	0.0312
	Multiple tumor	4.91853 (2.2445, 10.7785)	0.0001
DSS	Smoking habit (current)	0.98786 (0.3539, 2.7572)	0.9814
	Age (67 < yr)	0.37251 (0.0808, 1.7181)	0.2055
	Gender (male)	3.89167 (0.4809, 31.4908)	0.2027
	Alcohol abuse	0.98786 (0.3539, 2.7572)	0.3991
	Multiple tumor	7.08829 (2.2387, 22.4436)	0.0009

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.

Table 6 Comparison of clinicopathological factors per current smoking status in the hepatitis C virus-related hepatocellular carcinoma and hepatitis B virus-related hepatocellular carcinoma patient group

	HCV (n = 273)			HBV (n = 68)		
	Current (n = 88)	Never + Ex (n = 185)	P value	Current (n = 32)	Never + Ex (n = 36)	P value
Age (mean ± SD)	65.34 ± 7.82	68.02 ± 8.77	0.0153	53.66 ± 13.74	60.25 ± 10.46	0.0284
Gender (male/female)	81/7	122/63	< 0.0001	31/1	28/8	0.0204
Alcohol abuse (+/-)	35/53	28/157	< 0.0001	13/19	9/27	0.1692
Diabetes mellitus (+/-)	20/68	42/143	0.9964	5/27	7/29	0.6801
BMI (mean ± SD)	21.71 ± 2.74	22.87 ± 3.47	0.0031	23.01 ± 3.89	22.85 ± 3.77	0.8656
ICG R15 (%)	16.14 ± 7.24	19.81 ± 9.56	0.0005	12.54 ± 5.25	14.00 ± 7.11	0.3451
AFP (ng/mL), median (range)	20.5 (2, 29800)	29 (0, 19500)	0.4338	64.9 (1, 271600)	14.8 (2.4, 209900)	0.7995
Tumor size (mean ± SD mm)	39.25 ± 25.87	36.48 ± 25.52	0.4050	47.69 ± 29.26	51.53 ± 36.56	0.6369
Solitary/Multiple	60/28	122/63	0.7142	17/15	24/12	0.2546
Vp (+/-)	28/60	46/139	0.2271	13/19	16/20	0.7506
T factor (T12/T34)	48/40	108/77	0.5498	15/17	17/19	0.9772
Recurrence (+/-)	59/29	138/47	0.1934	20/12	20/16	0.5614

HCV: Hepatitis C virus; HBV: Hepatitis B virus; BMI: Body mass index; AFP: Alpha-fetoprotein.

covalently bind to DNA and form DNA adducts, which play a central role in the carcinogenic process by causing miscoding events in critical genes^[21]. One hypothesis is that in current smokers, these genetic abnormalities due to smoking are superimposed on the natural course of C-HCC and thus highly malignant HCC develops. We suspect that this hypothesis will be verified by further studies in the near future.

Another interesting result of the present study is that smoking status was not correlated with DFS in the C-HCC group. Although this may be explained by the carcinogenesis *via* chronic HCV infection, it seems to contradict our finding that smoking habit was significantly associated with disease-specific survival. Two hypotheses that may explain this contradiction are as follows: (1) The malignant potential of recurrent tumors in the current smokers was higher than that in the other patients; and (2) the number of cases that had relapsed as a metastatic lesion of the resected primary tumor was larger in the current-smoker group compared to the never + Ex-smoker group. To elucidate this point clearly, it is crucial to analyze surgical outcomes based on detailed information regarding post-surgery smoking

cessation. Quite regrettably, such data were not available in our database.

Although the inflammation and liver damage associated with chronic hepatitis B also introduce an accumulation of genetic and epigenetic alterations, a direct effect of HBV contributes to the development of B-HCC^[2]. HBV genomes can integrate into the host genome and induce chromosomal alterations and insertional mutagenesis of cancer genes^[22]. Therefore, B-HCC can develop in the absence of inflammation, which is in stark contrast to C-HCC development^[23]. The reason for the different association of smoking status and surgical outcomes between the B-HCC and C-HCC groups may be caused by the differences in carcinogenesis *via* HBV infection and HCV infection. However, a study based in China that analyzed the surgical outcomes of 302 patients with B-HCC reported that smoking status was correlated with both HCC recurrence and HCC mortality^[13]. Therefore, the reason why smoking status did not correlate with the surgical outcomes of B-HCC in the present study may be due simply to the small sample size of the B-HCC patients (n = 68, vs 273 C-HCC patients).

The results of our subgroup analyses of the C-HCC and B-HCC patients comparing the current-smoker patients and the other patients were also interesting. The analysis of the C-HCC group revealed that the current-smoker group developed HCC at significantly younger ages compared to the never+Ex group. The current-smoker group was similarly significantly younger in the B-HCC group. These results of the present study and our NBNC-HCC study^[11] both showed that current smokers develop HCC at a younger age than other patients, which suggests an additive effect of smoking on the development of HCC irrespective of the virus infection status.

The limitations of the present study are retrospective-designed study, the small number of patients, and the long study period for enrollment. Information regarding post-surgery smoking status and treatment procedure for recurrent tumor were not available. Although we believe that our results provide important information to elucidate HCC's natural history involving the patients' lifestyle, our findings should be verified by investigations that include detailed smoking information, in large retrospective or prospective studies.

In conclusion, our present findings indicate that a current-smoking habit is significantly correlated with the overall and disease-specific survivals of patients with C-HCC. In contrast, our B-HCC patient group showed a weak association between current smoking and surgical outcomes. Our analyses also revealed that the current smokers were significantly younger than the other patients irrespective of hepatitis viral infection status.

ARTICLE HIGHLIGHTS

Research background

Although cigarette smoking has been recognized as one of the risk factors for hepatocellular carcinoma (HCC), the surgical outcomes and clinicopathological characteristics according to smoking habits of HCC patients remains unclear. We investigate the association between smoking status and surgical outcomes in hepatitis B virus-related HCC (B-HCC) and HCV-related HCC (C-HCC).

Research motivation

We recently analyzed the relationship between smoking status and surgical outcomes in patients with non-B non-C (NBNC)-HCC, and our analysis revealed that smoking habits are significantly correlated with the curatively resected surgical outcomes of NBNC-HCC. We then speculated that if smoking habits truly affect the postoperative prognosis of HCC, smoking habits might also affect the postoperative prognosis of viral-associated HCC patients.

Research objectives

We conducted the present study to investigate the association between smoking habits and surgical outcomes in B-HCC and C-HCC patients who underwent curative surgery, and clarify the clinicopathological features associated with smoking habits in patients with B-HCC or C-HCC.

Research methods

Cases of the 341 consecutive patients with viral-associated HCC (C-HCC, $n = 273$; B-HCC, $n = 68$) who underwent curative surgery for their primary lesion were retrospectively examined. We categorized smoking status at the time of surgery into never, ex- and current smoker and analyzed the clinicopathological

features and surgical outcomes, *i.e.*, disease-free survival (DFS), overall survival (OS), and disease-specific survival (DSS).

Research results

The multivariate analysis in the C-HCC group revealed that current-smoker status was significantly correlated with both OS and DSS. No significant correlation was observed between current-smoker status and DFS, OS, or DSS in the B-HCC patients of the univariate or multivariate analyses.

Research conclusions

Smoking habit is significantly correlated with the overall and disease-specific survivals of patients with C-HCC, and in contrast, the B-HCC patients showed a weak association between smoking status and surgical outcomes.

Research perspectives

The results of this study support the hypothesis that smoking-associated HCC is with is high malignant potential. It would be a motivation for further research. We expect future research clarify the mechanism of carcinogenesis of HCC via smoking. Our results also can be expected to provide further motivation for smoking cessation.

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