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Effect of smoking on survival of patients with hepatocellular carcinoma

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Abstract

Background & Aims: Lifestyle factors such as smoking, obesity and physical activity have gained interest in the field of hepatocellular carcinoma. These factors play a significant role in the development of hepatocellular carcinoma. Several studies revealed the impact of tobacco consumption on the development of hepatocellular carcinoma and its synergistic effects with viral etiologies (hepatitis B and C). The effects of smoking on survival in patients with a diagnosed hepatocellular carcinoma have not yet been investigated in a Western cohort where hepatitis C infection is a major risk factor.

Methods: Using data from a prospective cohort of patients with hepatocellular carcinoma who were followed at the University Hospital of Bern, Switzerland, survival was compared by Kaplan–Meier analysis in smokers and nonsmokers, and multivariate Cox regression was applied to control for confounding variables.

Results: Of 238 eligible hepatocellular carcinoma patients, 64 were smokers at the time of inclusion and 174 were nonsmokers. Smokers had a significant worse overall survival than nonsmokers (hazard ratio 1.77, 95% confidence interval: 1.22-2.58, P=.003). Analysis of patients according to their underlying liver disease, revealed that smoking, and not nonsmoking, affected survival of hepatitis B virus and C virus-infected patients only. In this subgroup, smoking was an independent predictor for survival (hazard ratio 2.99, 95% confidence interval: 1.7-5.23, P<.001) and remained independently predictive when adjusted for confounding variables.

Conclusions: This study shows that smoking is an independent predictor of survival in hepatitis B virus/hepatitis C virus-infected patients with hepatocellular carcinoma.

KEYWORDS

hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, smoking, survival

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death.[1] More than 90% of HCCs are associated with a known risk factor: the most common causes of HCC are hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcohol-induced liver disease (AILD), nonalcoholic steatohepatitis (NASH) and haemochromatosis. While the etiologies for HCC are well-known, several studies suggest an association between lifestyle factors and HCC. For example, obesity and diabetes play a key role in NASH-associated HCC.[2] Other lifestyle factors such as physical activities or smoking have also been linked to HCC.[3] For the latter, several studies conducted in the United States,[4-6] in

Abbreviations: AILD, alcohol-induced liver disease; CI, confidence interval; CT, computer tomography; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MELD, Model For End-Stage Liver Disease; MRI, magnetic resonance imaging; NASH, nonalcoholic steatohepatitis; OS, overall survival; QOL, quality of life.

Europe,[7,8] and in Asia[9-13] demonstrated that smoking increases the risk of developing HCC. Among these studies, several reported a dose-dependent[5,7,9,10] and/or a duration-dependent association.[10,13] Interestingly, some of these studies reported a gender difference. Jee et al.[11] demonstrated an association between smoking and HCC development in men, but not in women. Likewise, Hassan et al.[4] found an increased risk of developing HCC in male, but not in female smokers, however, there was a synergistic effect between cigarette smoking and heavy alcohol consumption in women. Conversely, Evans et al.[14] found an association in women, but not in men. While most of the studies on this topic found an association between this risk factor and the development of HCC, one study found no association at all.[15]

Some studies have also investigated the particular association between smoking and viral-induced HCC. Franceschi et al.[16] found that smoking had an influence on the development of HCC only in hepatitis-infected patients, without distinction between HBV and HCV. Two studies found a synergistic effect between HCV infection and cigarette smoking in the development of HCC.[12,17] On the other hand, for hepatitis B infection, Jee et al.[11] found no synergistic effect with smoking. Kuper et al.[7] showed smaller associations between heavy smoking habits (>2 packs a day) and HCC development in patients with HBV or HCV infection (odds ratio 2.1 for viral-infected patients vs 2.8 for noninfected patients). The aim of the current study was to investigate the impact of cigarette smoking on the overall survival (OS) of patients with diagnosed HCC.

Key points

- The effect of smoking on overall survival in patients with hepatocellular carcinoma has been assessed using a Swiss prospective cohort.
- Smokers with hepatitis-virus induced hepatocellular carcinoma have a worse overall survival than nonsmokers.
- Smoking is an independent predictor for overall survival.
- It remains unclear if this result is because of faster progression of cirrhosis or HCC development, other lifestyle factors or patient poor compliance.

2 | PATIENTS AND METHODS

Data were taken from 240 patients who had entered the Bern HCC cohort, a prospective cohort, since August 1, 2010.[18,19] For inclusion into the Bern cohort, patients had to be >18 years old and were included in the cohort for ≤12 months after first diagnosis. Diagnosis of HCC was established according to the European Association for the Study of the Liver (EASL) clinical practice guidelines.[20] Noninvasive criteria were based on the presence of the typical radiological hallmarks of HCC, which included hypervascularity in the arterial phase with washout in the portal venous or delayed phase, using 4-phases multidetector computed tomography (CT) scanner and/or dynamic contrast-enhanced magnetic resonance imaging (MRI). Prospective information was collected in a standardized manner. Local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland) approved the protocol and patients provided informed consent.

At inclusion, 136 variables were gathered for each patient covering demographic, clinical, laboratory, radiological, treatment and quality of life (QoL) information. Patients were followed up every 3 months, where clinical, laboratory, radiological, treatment and QoL data were obtained.

All data were prospectively collected and retrospectively analysed. The OS of the whole cohort was assessed, stratified by smoking status. Overall survival was defined as the time from the date of the first diagnosis of HCC to the time of death, last follow-up evaluation, or the date of data censoring. Smoking was coded as a dichotomous variable, a patient being considered as a smoker when smoking at least once a day at the moment of inclusion. Overall survival in smokers and nonsmokers was also assessed in a subgroup of patients with and without HBV/HCV-induced HCC.

Cumulative survival rates were calculated by the Kaplan–Meier method and survival curves were compared by the log-rank test. Cox proportional hazard regressions were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Clinical and laboratory characteristics between two sets of patients were compared using Pearson chi-square test for categorical variables, the Kruskal–Wallis test for continuous variables. All analyses were conducted using R version 3.1.1.[21] A P value of <.05 was considered as statistically significant.

3 | RESULTS

A total of 238 eligible adult HCC patients were included; of whom, 64 patients were smokers and 174 were nonsmokers at the time of inclusion into the Bern cohort. Demographic, clinical and tumour characteristics of these two groups are summarized in Table 1. The median (range) age at presentation was 65 (25-88) years, and the majority (85.7%) of patients were male. Etiology of HCC was AILD for 103 patients (43.3%), HCV for 67 patients (28.2%), HBV for 46 patients (19.3%), NASH for 75 patients (31.5%) and haemochromatosis for 18 patients (7.6%). A total of 81.4% of patients had a cirrhotic liver; of whom, 65.8%, 29.5% and 4.7% were Child-Pugh A, B and C respectively. Tumours were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system[20]: 13 (5.5%) were stage 0, 83 (34.9%) stage A, 80 (33.6%) stage B, 45 (18.9%) stage C and 17 (7.1%) stage D.

No difference was found between the two groups (smokers vs nonsmokers) for gender, BCLC stage, Child-Pugh class, Model For End-Stage Liver Disease (MELD) score, Bilirubin, alpha foetoprotein (AFP) or treatment. There were differences for the etiologies: AILD (P<.001), HBV (P=.002) and HCV (P<.001) were more frequent in smokers while NASH (P=.004) was more frequent in nonsmokers. Significant differences were also found for age, with smokers being younger than nonsmokers (medians, 59 vs 66 years, P<.001) and for comorbidities: whereby more smokers were consuming alcohol (defined as >30 g/day, P<.001) while nonsmokers were more likely to have diabetes

TABLE 1 Demographic, clinical and tumour characteristics of all smokers and nonsmokers with hepatocellular carcinoma (HCC) from the whole cohort

	Smokers n=64		Non-smokers n=174		
	n	%	n	%	*P* value
Age[a]	59	—	66	—	<.001
Gender					
Male	54	84.4	150	86.2	.682
Female	10	15.6	24	13.8	
BMI[a]	25.85	—	26.5	—	.445
BCLC					
0	4	6.3	9	5.2	.359
A	22	34.4	61	35.1	
B	16	25.0	64	36.8	
C	16	25.0	29	16.7	
D	6	9.4	11	6.3	
Child-Pugh Grade[b]					
A	36	59.0	91	68.9	.362
B	21	34.4	36	27.3	
C	4	6.6	5	3.8	
MELD[a]	9		8		.238
Bilirubin (μmol/L) [a]	19.0	—	18.0	—	.359
INR[a]	1.18	—	1.12	—	.023
Platelets (g/L)[a]	91	—	144	—	.043
AFP (kU/L)[a]	9.8	—	11.0	—	.669
Treatment					
Resection	9	14.1	42	24.3	.089
LT	6	9.4	19	11.0	.721
TACE	21	32.8	63	36.4	.607
RFA	4	6.3	8	4.6	.612
SIRT	4	6.3	18	10.4	.328
Systemic	9	14.1	23	13.3	.878
Etiology[c]					
Alcohol	42	65.6	61	35.5	<.001
HBV	21	32.8	25	14.6	.002
HCV	30	46.9	37	21.4	<.001
NASH	11	17.2	64	37.0	.004
Haemochromatosis	2	3.1	16	9.3	.167
Comorbidity					
Diabetes	13	20.3	63	36.6	.017
Alcohol[d]	18	28.1	15	8.7	<.001
Survival					
Observation time (days)[a]	489	—	653	—	.032
Median survival time (days)	547	—	1170	—	.002
Mortality	42	65.6	79	45.4	.008

AFP, alpha foetoprotein; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; LT, Liver transplantation; MELD, Model For End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

[a]Median value.

[b]Child-Pugh calculated only for cirrhotic patients.

[c]Patients can have multiple etiologies.

[d]Defined as >30 g/day.

mellitus type 2 (*P*=.017). There were also significant differences for INR (1.18 for smokers vs 1.12 for nonsmokers, *P*=.023) and for platelets (91 g/L for smokers vs 144 g/L for nonsmokers, *P*=.043).

Overall survival was significantly worse for smokers compared with nonsmokers (HR: 1.77, 95% CI: 1.22-2.58; *P*=.003) (Figure 1A). Smokers also had worse OS than nonsmokers in the HBV/HCV-induced HCC subgroup, with greater separation between smokers and nonsmokers than was observed in the analysis of the whole cohort (HR: 2.99, 95% CI: 1.7-5.23; *P*<.001) (Figure 1B). No difference between smokers and nonsmokers was shown in patients with nonviral-induced HCC (HR: 1.05, 95% CI: 0.57-1.92, *P*=.877).

We calculated univariate Cox regression models considering smoking but also other possible factors, including age, gender, BMI, BCLC stage, Child-Pugh point, MELD, bilirubin, INR, platelets, AFP, diabetes or alcohol consumption. Four factors were significantly associated with survival: smoking (HR: 2.99, 95% CI 1.70-5.23, *P*<.001), gender (HR: 2.52, 95% CI: 1.30-4.88, *P*=.006), BCLC stage (HR: 3.29, 95% CI: 2.38-4.55, *P*<.001), Child-Pugh points (HR: 1.42, 95% CI: 1.15-1.77, *P*=.001). Calculating a multivariate Cox regression model including all significant factors from the univariate analysis, we found that smoke (HR: 2.41, 95% CI: 1.28-4.55, *P*=.007) and BCLC stage (HR: 2.73 95% CI: 1.93-3.85, *P*<.001) were significant independent predictors, while gender (HR: 2.02, 95% CI: 0.98-4.18, *P*=.057) and Child-Pugh points (HR: 1.10, 95% CI: 0.89-1.35, *P*=.404) were not (Table 2).

Furthermore, we did a subgroup analysis on patients who did not undergo a curative therapy (ie, we excluded patients who got resection, ablation or liver transplantation). In that subgroup, Kaplan–Meier analysis reveals that smokers still have a significant worse survival than nonsmokers (*P*=.004). Cox regression shows that smoking is a significant predictor also in that subgroup (HR: 2.47, 95% CI: 1.30-4.69, *P*=.006).

Finally, we also analysed the cause of death in both group. There was no statistical difference in the cause of death between smoker and nonsmoker (*P*=.089). Most of the patients died either from HCC or from hepatic insufficiency and no patients died from a cardiovascular event (defined as myocardial infarct or stroke) in both group (Table S1).

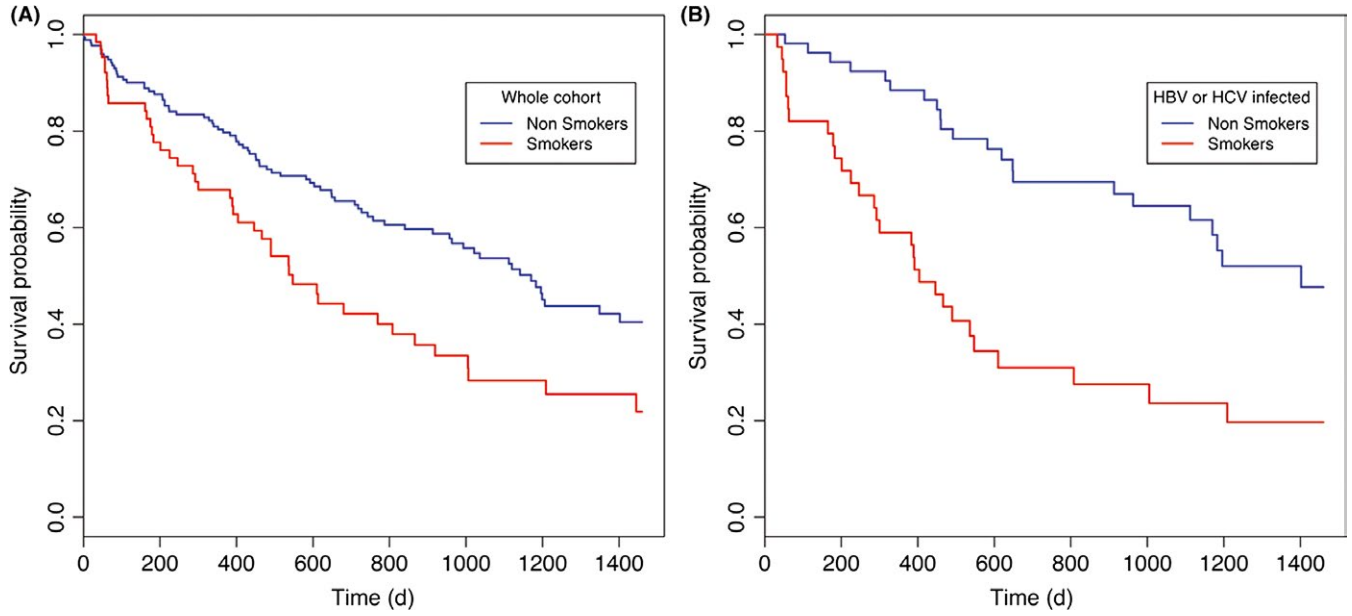

FIGURE 1 (A) Kaplan–Meier analysis for overall survival in the whole cohort of patients with hepatocellular carcinoma (HCC) who were smokers (n=64) and non-smokers (n=174) (***P***=.003). (B) Kaplan-Meier analysis for overall survival in the subgroup of patients with hepatitis B or C virus-induced HCC who were smokers (n=39) and non-smokers (n=54) (***P***<.001)

TABLE 2 Univariate and multivariate Cox-Regression for the patients with hepatitis B or C co-infection

	Univariate			Multivariate[a]		
Factor	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Smoking	2.99	1.70-5.23	<.001	2.41	1.28-4.55	.007
Age	0.98	0.95-1.01	.173	—	—	—
Gender	2.52	1.30-4.88	.006	2.02	0.98-4.18	.057
BMI	1.01	0.94-1.07	.867	—	—	—
BCLC	3.29	2.38-4.55	<.001	2.73	1.93-3.85	<.001
Child-Pugh points	1.42	1.15-1.77	.001	1.10	0.89-1.35	.404
MELD	1.02	0.94-1.10	.663	—	—	—
Bilirubin	1.02	0.99-1.04	.169	—	—	—
INR	1.82	0.45-7.37	.404	—	—	—
Platelets	1.00	1.00-1.01	.533	—	—	—
AFP	1.00	1.00-1.00	.608	—	—	—
Diabetes	1.34	0.65-2.76	.424	—	—	—
Alcohol[b]	1.06	0.5-2.26	.878	—	—	—

AFP, alpha foetoprotein; BMI, body mass index; BCLC, Barcelona Clinic Liver Cancer; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]Variables that were significant predictors in the univariate regression were included in the multivariate regression.
[b]Defined as >30 g/day.

4 | DISCUSSION

Increasing attention is being given to the association between HCC and lifestyle factors, such as obesity, physical activity and smoking habit. Using the Bern HCC cohort, and comparing smokers with nonsmokers, the latter were shown to have a significantly better OS than smokers. Analysis of the patients according their underlying liver disease, smoking appears to confer worsened survival for hepatitis-infected patients only. In HBV/HCV-infected patients, differences were found for age, liver transplantation rate and alcohol consumption between smokers and nonsmokers. However, by Cox regression analysis, smoking remained a significant predictor for OS when adjusted for potential confounding factors, including age, gender, tumour stage, Child-Pugh class, diabetes, alcohol consumption and treatment options. While some studies suggest that gender could influence the association between smoking and HCC development,[4,11,14] our study

showed that smoking is associated with a worse survival in both genders. Smoking is, therefore, an independent predictor for OS in patients with viral-induced HCC in this cohort. This result is relevant since almost 80% of the worldwide HCC is attributable to HBV or HCV infection.[22]

A possible explanation for this important difference in survival rates among smokers and nonsmokers requires investigation. Several hypotheses can be formulated to explain this, among them a faster progression of cirrhosis, faster progression of HCC development, lifestyle variables that were not gathered in the study, or patient poor compliance. For the first possibility, it has indeed been demonstrated that smoking increases fibrosis in patients with HCV infection.[23,24] In the current cohort, smokers were younger than nonsmokers, a fact that supports the hypothesis of a faster progression of cirrhosis. In favour of the second possibility is the established fact that smoking tends to play a role in the development of various cancers. Covalent bonding of a carcinogenic substance to DNA to cause permanent mutations in essential genes of somatic cells is the foremost known pathophysiological pathway of smoking-induced cancer.[25] It remains unclear if there is a specific pathway that promotes a more rapid development of HCC in smoking patients with hepatitis infection, but the fact that smokers are younger in our cohort could support this hypothesis. Concerning the third possibility, some lifestyle variables that were not gathered in this cohort could influence survival. Indeed, it has been shown that smokers have worse fitness than nonsmokers.[26] Since exercise capacity—which was not measured in this cohort—is an important risk factor for all-cause mortality,[27] it would be interesting to explore this further. Finally, it has been suggested that smokers may be less compliant patients than nonsmokers,[28] which could also, in part, explain their worsened survival.

While this study shows a strong association between smoking and survival in patients with HCC, it has some limitations. We were unable to assess if there was a dose- or a duration-dependent effect of smoking on the survival. One could also argue that the effect of smoking is a confounding factor, but the outcome was adjusted for most of the demographic, clinical and tumour factors that have could influenced survival. The current analysis did not investigate whether smoking cessation after HCC diagnosis improves OS compared with patients who do not quit, which has been shown to be the case in lung cancer[29]; therefore, this should be addressed by future study.

This current analysis has built on the findings from previous studies that uncovered an association between smoking and HCC development, by demonstrating that OS is worse in HBV/HCV-infected smokers with diagnosed HCC. Based on these findings, smoking cessation should be considered for incorporation into the disease management for patients with HBV or HCV.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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