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

Author contributions: Kai K, the main author of this article, designed the study, conducted the data collection, and contributed to the statistical analyses; Komukai S and Kawaguchi A performed the statistical analyses; Koga H, Yamaji K, and Ide T contributed to the data collection; Aishima S and Noshiro H contributed to the data collection and reviewed the manuscript; all authors have read and approved the final manuscript.

Data sharing statement: No additional data are available.

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

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Kai K, Komukai S, Koga H, Yamaji K, Ide T, Kawaguchi A, Aishima S, Noshiro H. Correlation between smoking habit and surgical outcomes on viral-associated hepatocellular carcinomas.
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, located on the island of Kyushu, the southwestern-most of Japan’s main islands) were initially enrolled in the study. Definition of the HBV infection and HCV infection was made on the basis of clinical symptoms, medical and laboratory 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 TNM 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 χ² 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
The factors found to be significantly correlated with disease-specific survival were smoking (current vs other; $P = 0.0483$), tumor size ($P = 0.0070$), $V_p$ ($P = 0.0177$), 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

The results of the univariate analyses for surgical outcomes in 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 were significantly larger than those of the B-HCC group (mean tumor sizes 49.72 mm vs 37.37 mm, $P = 0.0052$), and the percentage of $V_p$ was significantly higher in the B-HCC group compared to the C-HCC group (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).

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 $V_p$ was significantly higher in the B-HCC group compared to the C-HCC group (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).

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

|                      | HCV ($n = 273$) | HBV ($n = 68$) | $P$ 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    | 22.91 ± 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, 29803) | 31 (1, 271600) | 0.0025    |
| 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)     |           |
| $V_p$ (+)            | 74 (27.11)      | 29 (42.65)     | 0.0125    |
| (-)                  | 199 (72.89)     | 39 (57.35)     |           |
| $T$ factor           |                 |                |           |
| $T_1/2$              | 156 (57.14)     | 32 (47.06)     | 0.1347    |
| $T_3/4$              | 117 (42.86)     | 36 (52.94)     |           |

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

| Characteristics           | DFS          |          | OS          |          | DSS          |          |
|---------------------------|--------------|----------|-------------|----------|--------------|----------|
|                           | $n$          | HR (95%CI) | $P$ value   | HR (95%CI) | $P$ value   | HR (95%CI) | $P$ value |
| Age                       |              |           |             |          |              |          |
| $\leq 67$                  | 133          | 1        | 0.9234      | 1        | 0.5143       | 1        | 0.7101    |
| $> 67$                    | 140          | 1.01381 (0.7665, 1.3409) | 1.10679 (0.8159, 1.5015) | 0.92155 (0.599, 1.4177) |
| Gender                    |              |           |             |          |              |          |
| Female                    | 70           | 1        | 0.3699      | 1        | 0.5110       | 1        | 0.2434    |
| Male                      | 203          | 0.91269 (0.666, 1.2508) | 1.12916 (0.786, 1.6221) | 1.38666 (0.8019, 2.3876) |
| Smoking habit (Ex + current) |        |           |             |          |              |          |
| Absent                    | 111          | 0.5978   | 1           | 0.1262   | 1            | 0.2147   |
| Present                   | 162          | 0.92696 (0.6994, 1.2286) | 1.27849 (0.9332, 1.7516) | 1.32797 (0.8483, 2.0788) |
| Smoking habit (current)    |              |           |             |          |              |          |
| Absent                    | 185          | 1        | 0.8664      | 1        | 0.0144       | 1        | 0.0483    |
| Present                   | 88           | 1.02258 (0.7527, 1.3892) | 1.47783 (1.0808, 2.0207) | 1.55795 (1.0333, 2.4192) |
| Alcohol abuse              |              |           |             |          |              |          |
| Absent                    | 210          | 1        | 0.0321      | 1        | 0.8232       | 1        | 0.7027    |
| Present                   | 63           | 0.68132 (0.4797, 0.9678) | 0.95952 (0.6677, 1.3788) | 0.90325 (0.5356, 1.5232) |
| Diabetes mellitus          |              |           |             |          |              |          |
| Absent                    | 211          | 1        | 0.3149      | 1        | 0.5259       | 1        | 0.9487    |
| Present                   | 62           | 1.16657 (0.85, 1.6564) | 1.12207 (0.7861, 1.6017) | 0.98302 (0.5831, 1.6572) |
| BMI                       |              |           |             |          |              |          |
| $\leq$ Median             | 137          | 0.0270   | 1           | 0.2082   | 1            | 0.6409   |
| $>$ Median                | 136          | 0.72863 (0.5593, 0.9647) | 0.82193 (0.6596, 1.1155) | 0.9026 (0.5868, 1.3884) |
| ICG R15 (%)               |              |           |             |          |              |          |
| $\leq$ Median             | 111          | 0.0088   | 1           | 0.2391   | 1            | 0.6896   |
| $>$ Median                | 162          | 1.47199 (1.1021, 1.9659) | 1.20762 (0.8825, 1.65) | 1.09334 (0.7056, 1.6941) |
| AFP                       |              |           |             |          |              |          |
| $\leq$ Median             | 136          | 0.2274   | 1           | 0.0402   | 1            | 0.1371   |
| $>$ Median                | 137          | 1.18795 (0.8981, 1.5713) | 1.37689 (1.0144, 1.8689) | 1.38776 (0.901, 2.1376) |
| Tumor size                |              |           |             |          |              |          |
| $\leq$ Median             | 161          | 0.0305   | 1           | 0.0019   | 1            | 0.0070   |
| $>$ Median                | 112          | 1.37235 (1.0303, 1.828) | 1.63014 (1.1982, 2.2178) | 1.81608 (1.1773, 2.8016) |
| Solitary/Multiple         |              |           |             |          |              |          |
| Solitary                  | 182          | 0.0021   | 1           | 0.0001   | 1            | 0.1182   |
| Multiple                  | 91           | 1.59365 (1.1835, 2.1459) | 1.8536 (1.3563, 2.5332) | 1.43932 (0.9115, 2.2728) |
| Vp                        |              |           |             |          |              |          |
| Absent                    | 199          | 0.0767   | 1           | 0.0004   | 1            | 0.0177   |
| Present                   | 74           | 1.33528 (0.9695, 1.839) | 1.81728 (1.3073, 2.5262) | 1.76737 (1.104, 2.8294) |
| T12/T34                   |              | $< 0.0001$ | 1           | 0.0008   | 1            | 0.315    |
| T12                       | 156          | 1        | 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.
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 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 <)               | 1.99531 (1.1763, 2.1635) | 0.0027       |
|      | T factor (T3/4)                  | 1.90638 (1.4279, 2.5452) | < 0.0001     |
| OS   | Smoking habit (current)          | 1.69259 (1.1844, 2.4187) | 0.0099       |
|      | 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       |
|      | ICG R15 (median <)               | 1.32015 (0.9524, 1.83)  | 0.0955       |
|      | T factor (T3/4)                  | 1.74555 (1.2767, 2.3865) | 0.0005       |
| DSS  | Smoking habit (current)          | 1.68394 (1.0201, 2.7798) | 0.0416       |
|      | Age (67 < yr)                    | 1.00355 (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 <)                   | 0.90781 (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.
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

| Characteristics                  | DFS          | OS           | DSS          |
|----------------------------------|--------------|--------------|--------------|
| Age                              |              |              |              |
| ≤ 67                             | 0.9417       | 0.8991       | 0.3769       |
| > 67                             | 0.97131      | 1.05615      | 0.5123       |
| Gender                           | 0.6063       | 0.1844       | 0.3363       |
| Female                           |              |              |              |
| Male                             | 1.28118      | 2.64152      | 2.70202      |
| Smoking habit (Ex + current)     | 0.8323       | 0.5660       | 0.9544       |
| Absent                           | 0.93056      | 1.26612      | 0.96953      |
| Present                          | 0.4008       | 0.3620       | 0.8001       |
| Smoking habit (current) Absent    |              |              |              |
| Present                          | 1.13047      | 1.38988      | 1.13501      |
| Alcohol abuse                    | 0.0183       | 0.0706       | 0.5674       |
| Absent                           | 1.41390      | 0.45823      | 0.73339      |
| Present                          | 0.4682       | 0.6700       | 0.8752       |
| Diabetes mellitus                |              |              |              |
| Absent                           | 0.33766      | 0.9126      | 0.6383       |
| Present                          | 1.32065      | 1.21313      | 1.10618      |
| BMI ≤ Median                     |              |              |              |
| > Median                         | 1.3863       | 0.96125      | 1.26746      |
| ICG R15 (%) ≤ Median             | 1.38516      | 1.07744      | 1.38526      |
| AF ≤ Median                      | 0.0065       | 0.0015       | 0.0114       |
| > Median                         | 1.80218      | 3.54578      | 4.36412      |
| Tumor size ≤ Median              | 1.67393      | 1.61822      | 3.37156      |
| > Median                         | 0.1252       | 0.2124       | 0.0001       |
| Solitary/Multiple                | 0.0002       | 0.0001       | 0.0013       |
| Solitary                         | 3.30417      | 4.6829       | 6.42975      |
| Multiple                         | 0.0598       | 0.0035       | 0.0362       |
| Vp Absent                        | 1.85208      | 2.94188      | 2.92487      |
| Present                          | 27           | 4.6829       | 6.42975      |
| T12/T34                          | 0.0042       | 0.0001       | 0.0019       |
| T12                              | 32           | 2.60213      | 5.55785      |
| T34                              | 36           | 2.5342       | 10.58522     |

DFS: Disease-free survival; OS: Overall survival; DSS: Disease-specific survival.
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\cite{16}. Activated inflammatory cells release reactive oxygen species and induce lipid peroxidation, which promotes a pro-oncogenic environment and DNA damage\cite{17} and increases DNA methylation\cite{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\cite{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) | 0.0044  |
| OS       | Smoking habit (current)          | 1.43613 (0.6685, 3.0045) | 0.3365  |
|          | Age (67 < yr)                    | 0.88973 (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 (0.0801, 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 (2.2937, 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

|          | Current (n = 273) | 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 | 0.0155 |         | 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, 209900) | 0.7995 |
| Tumor size (mean ± SD mm) | 39.25 ± 25.87 | 36.48 ± 25.52 | 0.4650 |         | 47.69 ± 29.26 | 51.33 ± 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[23]. 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.[23]. 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 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 analyses.

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.

**REFERENCES**

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]
2. Ringelhan M, McKeating JA, Potzer U. Viral hepatitis and liver cancer. Philos Trans R Soc Lond B Biol Sci 2017 [PMID: 28893941 DOI: 10.1098/rstb.2016.0274]
3. Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. J Gastroenterol 2009; 44 Suppl 19: 102-107 [PMID: 19148882 DOI: 10.1007/s00535-008-2251-0]
4. But DY, Lai CL, Yuan MF. Natural history of hepatitis-related hepatocellular carcinoma. World J Gastroenterol 2008; 14: 1652-1656 [PMID: 18350595 DOI: 10.3748/wjg.14.1652]
5. Zhou Y, Si X, Wu L, Su X, Li B, Zhang Z. Influence of viral hepatitis status on prognosis in patients undergoing hepatic resection for hepatocellular carcinoma: a meta-analysis of observational studies. World J Surg Oncol 2011; 9: 108 [PMID: 21933440 DOI: 10.1186/1477-7819-9-108]
6. Utsunomiya T, Shimada M, Kudo M, Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, Takayama T, Kokudo N; Liver Cancer Study Group of Japan. A comparison of the surgical outcomes among patients with HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: a nationwide study of 11,950 patients. Ann Surg 2015; 261: 513-520 [PMID: 25072437 DOI: 10.1097/SLA.0000000000000821]
7. Tateishi R, Okazawa T, Fujisawa N, Oikawa K, Kiyosawa K, Omata M, Kumada H, Hayashi N, Koik K. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. J Gastroenterol 2015; 50: 350-360 [PMID: 24929638 DOI: 10.1007/s00535-014-0973-8]
8. Hara M, Tanaka K, Sakamoto T, Hijiki Y, Mizuta T, Eguchi Y, Yasutake T, Ozaki I, Yamamoto K, Onohara S, Kawazoe S, Shigematsu H, Koizumi S. Case-control study on cigarette smoking and the risk of hepatocellular carcinoma among Japanese. Cancer Sci 2009; 99: 93-97 [PMID: 17956590]
9. Tanaka K, Tsuji I, Waki K, Nagata C, Mizoue T, Inoue M, Tsugane S; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. Jpn J Clin Oncol 2006; 36: 445-456 [PMID: 16782973 DOI: 10.1093/jjco/hyl040]
10. Koh WP, Robin K, Wang R, Govindarajan S, Yuan JM, Yu MC. Smoking as an independent risk factor for hepatocellular
Kai K et al. Smoking and surgical outcomes of viral-associated HCC

carcinoma: the Singapore Chinese Health Study. Br J Cancer 2011; 105: 1430-1435 [PMID: 21915129 DOI: 10.1038/bjc.2011.360]

11 Kai K, Koga H, Aishima S, Kawaguchi A, Yamaji K, Ide T, Ueda J, Noshiro H. Impact of smoking habit on surgical outcomes in non-B non-C patients with curative resection for hepatocellular carcinoma. World J Gastroenterol 2017; 23: 1397-1405 [PMID: 28293086 DOI: 10.3748/wjg.v23.i8.1397]

12 Abdel-Rahman O, Helbling D, Schöb O, Eltobgy M, Mohamed H, Schmidt J, Giryes A, Mehrabi A, Iype S, John H, Tekbas A, Zidan A, Oweira H. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies. J Evid Based Med 2017; 10: 245-254 [PMID: 28891275 DOI: 10.1111/jebm.12270]

13 Zhang XF, Wei T, Liu XM, Liu C, Lv Y. Impact of cigarette smoking on outcome of hepatocellular carcinoma after surgery in patients with hepatitis B. PLoS One 2014; 9: e85077 [PMID: 24454795 DOI: 10.1371/journal.pone.0085077]

14 Lv Y, Liu C, Wei T, Zhang JF, Liu XM, Zhang XF. Cigarette smoking increases risk of early morbidity after hepatic resection in patients with hepatocellular carcinoma. Eur J Surg Oncol 2015; 41: 513-519 [PMID: 25656703 DOI: 10.1016/j.ejso.2015.01.015]

15 Mangus RS, Fiddrell JA, Kubal CA, Loefler AL, Krause AA, Bell JA, Tiwari S, Tector J. Worse Long-term Patient Survival and Higher Cancer Rates in Liver Transplant Recipients With a History of Smoking. Transplantation 2015; 99: 1862-1868 [PMID: 26308417 DOI: 10.1097/TP.0000000000000671]

16 Trinchet JC, Game-Carré N, Nahon P, N’kontcho G, Beaugrand M. Hepatocellular carcinoma in patients with hepatitis C virus-related chronic liver disease. World J Gastroenterol 2007; 13: 2455-2460 [PMID: 17552029 DOI: 10.3748/wjg.v13.i7.2455]

17 Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. Langenbecks Arch Surg 2006; 391: 499-510 [PMID: 16909291]

18 Shih YL, Kuo CC, Yan MD, Lin YW, Hsieh CB, Hsieh TY. Quantitative methylation analysis reveals distinct association between PAX6 methylation and clinical characteristics with different viral infections in hepatocellular carcinoma. Clin Epigenetics 2016; 8: 41 [PMID: 27110298 DOI: 10.1186/s13148-016-0208-3]

19 Okamoto Y, Shinjo K, Shimizu Y, Sano T, Yamao K, Gao W, Fujii M, Osada H, Sekido Y, Mutakami S, Tanaka Y, Joh T, Sato S, Takahashi S, Wakita T, Zhu J, Issa JP, Kondo Y. Hepatitis virus infection affects DNA methylation in mice with humanized livers. Gastroenterology 2014; 146: 562-572 [PMID: 24184133 DOI: 10.1053/j.gastro.2013.10.056]

20 El-Zayadi AR. Heavy smoking and liver. World J Gastroenterol 2006; 12: 6098-6101 [PMID: 17036378 DOI: 10.3748/wjg.v12.i38.6098]

21 Hecht SS. Lung carcinogenesis by tobacco smoke. Int J Cancer 2012; 131: 2724-2732 [PMID: 22945513 DOI: 10.1002/ijc.27816]

22 Fattovich G, Strufolino T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004; 127: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

23 Buendia MA, Neuveut C. Hepatocellular carcinoma. Cold Spring Harb Perspect Med 2015; 5: a021444 [PMID: 25646384 DOI: 10.1101/cshperspect.a021444]

P-Reviewer: Yu WB  S-Editor: Chen K L-Editor: A E-Editor: Huang Y
