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Heavy Smoking Increases Early Mortality Risk in Patients with Hepatocellular Carcinoma after Curative Treatment

Running title: Smoking and HCC survival

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Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular
carcinoma; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; OS, overall survival; RFA, radiofrequency ablation; RMST, Restricted Mean Survival Time; RMTL, Restricted Mean Time Lost

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Abstract

**Background:** Although cigarette smoking has been associated with an increased risk of hepatocellular carcinoma (HCC), its association with HCC mortality remains underexplored. We aimed to evaluate the effect of smoking on early mortality in HCC patients following curative treatment.

**Methods:** Data from the Korean Primary Liver Cancer Registry were examined for HCC patients who underwent liver resection or radiofrequency ablation between 2015 and 2018. Smoking cumulative dose was assessed in pack-years. The primary outcome was the 3-year overall survival (OS).

**Results:** Among 1924 patients, 161 were classified as heavy smokers (≥ 40 pack-years). Heavy smokers exhibited a lower 3-year survival rate (77.1%) than nonsmokers (83.3%), with a significant difference observed in the 3-year OS (p = 0.016). The assessment of smoking pack-years in relation to 3-year OS revealed a dose-dependent pattern, with the hazard ratio exceeding 1.0 at 20 pack-years and continuing to rise until 40 pack-years, reaching peak at 1.21 (95% confidence interval: 1.01, 1.45). Multivariate Cox-regression analysis revealed heavy smoking, age ≥ 60 y, underlying cirrhosis, tumor size > 3 cm, vascular invasion, and Child-Pugh class B/C as risk factors for 3-year OS. Subgroup analyses of patients with a tumor size < 3 cm, absence of vascular invasion, and meeting the Milan criteria also showed inferior outcomes for heavy smokers in all three subgroups.

**Conclusion:** Heavy smoking, defined as a history of > 40 pack-years, was linked to poorer 3-year survival outcomes in HCC patients undergoing curative treatments, underscoring the importance of smoking cessation in this population.

**Key words:** Smoking, overall survival, liver resection, radiofrequency ablation, hepatocellular
carcinoma
Introduction

Liver cancer is the third leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) accounting for the majority of liver cancer.\(^1\) Despite recent advancements in immunotherapy for HCC, the prognosis for advanced stages remains challenging.\(^2\) Contrastingly, the prognosis for early stage HCC is often favorable as it can be effectively treated with curative intent using modalities such as radiofrequency ablation (RFA) or surgical resection.\(^3,5\)

Although early stage HCC exhibits a promising perspective, patients undergoing curative treatment remain susceptible to HCC recurrence or de novo HCC. Therefore, vigilant post-treatment surveillance is imperative to improve patient prognosis.\(^6,7\) Additionally, numerous factors, including host and tumor conditions, have been implicated in influencing prognosis following curative treatment.\(^8,9\) Modifiable host factors such as the body mass index (BMI), diabetes mellitus, and alcohol consumption have been extensively studied and identified as influential factors in HCC prognosis.\(^10-12\) Therefore, modifying these potential prognostic factors within patient control has emerged as a crucial strategy for enhancing the prognosis.

Cigarette smoking is one of the factors that has been studied for its possible association with HCC. Previous studies have linked smoking to an increased risk of HCC, and smoking cessation has been shown to reduce this risk.\(^13,14\) Smoking is widely recognized as a potential risk factor for mortality in patients with HCC.\(^15,16\) Furthermore, a possible association between smoking and early morbidity after liver resection has been reported.\(^17\) These findings underscore the significance of smoking in the prognosis of HCC and emphasize the need for additional studies to explore the impact of smoking on more specific subgroups of patients with HCC.
While few studies have suggested a potential link between smoking and HCC prognosis, others report contrasting results indicating no association between smoking and HCC prognosis. Moreover, its direct association with the prognosis after curative treatment has not been extensively explored, highlighting the need for further investigation. Therefore, our study aimed to elucidate the association between smoking and HCC prognosis in terms of overall survival (OS) after curative treatment and to examine the dose-response relationship between smoking and mortality following curative resection.

Methods

Patients

Data were obtained from the Korean Primary Liver Cancer Registry (KPLCR), a repository of randomly selected hospital-based data pertaining to patients with HCC, representing approximately 15% of the HCC patients registered in the Korean Central Cancer Registry. Baseline data of patients with HCC who underwent liver resection or RFA between January 1, 2015, and December 31, 2018, were collected and followed up until 2021. HCC was diagnosed on the basis of histological or radiological examinations, including computed tomography and/or magnetic resonance imaging. Patients were excluded from the study for the following reasons: (1) Follow-up period less than 1 month, (2) Presence of extrahepatic metastasis, (3) Patients who received combination treatment with other treatment modalities, and (4) Absence of data regarding smoking history and/or laboratory findings. This study was approved by the Institutional Review Board of Incheon Saint Mary’s Hospital, The Catholic University of Korea (OC22ZIDI0160), and adhered to the principles outlined in the Declaration
of Helsinki. Given the retrospective nature of this study, the requirement for informed consent was waived.

**Study outcomes**

The primary endpoint was the 3-year OS from the time patients underwent either RFA or resection, while concurrently examining the impact of smoking on the 3-year OS. The 3-year OS was calculated from the date of RFA or resection until the occurrence of death or the last follow-up day, whichever was later. Survival data were censored in cases in which no mortality events were observed within a 3-year timeframe.

**Clinical and imaging variables**

Baseline characteristics of patients undergoing either RFA or resection, including age, sex, height, weight, comorbidities, smoking history, alcohol history, HCC etiology, serum alpha-fetoprotein (AFP) level, Child-Pugh score, laboratory findings, tumor size, tumor number, and the presence of vascular invasion, were obtained from the KPLCR database.

**Definition of smoking**

The history of smoking was collected in terms of duration of smoking and dose per day and summarized as pack-years for analysis. Patients were categorized based on pack-years of smoking into non-smokers, light smokers (< 20 pack-years), moderate smokers (20–40 pack-years), and heavy smokers (≥ 40 pack-years), with reference to previous studies.\(^{20,21}\)

**Statistical analysis**

Continuous variables were analyzed using Student’s t-test and are presented as mean values with standard deviations. Categorical variables were analyzed using the chi-squared test.
Survival analyses were conducted using the Kaplan–Meier method, and differences were assessed using the log-rank test. The Restricted Mean Survival Time (RMST) and Restricted Mean Time Lost (RMTL) were used to evaluate and compare survival outcomes between the groups. RMST was calculated as the area under the Kaplan-Meier curve, whereas RMTL was calculated as the area above the curve. Cox regression analyses were performed to identify factors associated with survival outcomes, with factors exhibiting p < 0.05 in univariate analysis included in multivariate analysis. Restricted cubic spline was applied to estimate the trend of the dose-response association between pack-years of smoking and the 3-year OS. Statistical significance was set at p < 0.05. All analyses were conducted using the R statistical software (version 4.0.3; R Foundation Inc., Vienna, Austria; http://cran.r-project.org, accessed on April 10, 2024).

Results

Baseline characteristics

A total of 2024 patients with HCC underwent either RFA or surgical resection during the study period. After excluding those who met the exclusion criteria, 1924 patients were included in the analysis (Figure 1). Table 1 presents the baseline characteristics of the enrolled patients. The mean age of the study population was 61.1 years, with a predominance of the male sex (78.6%). Viral hepatitis was the most common cause of HCC (52.8%), followed by alcohol (31.2%) and nonalcoholic fatty liver disease (NAFLD) (16.0%). Regarding the tumor status, 87.0% of the patients exhibited a single tumor mass, with a maximal tumor size of 34.6 mm, while 5.0% of the patients presented with vascular invasion. Most patients had Child-Pugh class A disease (92.9%), and the mean MELD score was 8.2. Regarding the treatment modality,
30.5% of the study cohort underwent RFA, while 69.5% underwent surgical resection.

Patients were subsequently categorized into heavy smoking (+) (n = 161) and heavy smoking (-) (n = 1763) groups based on a smoking history of ≥ 40 pack-years. When comparing baseline demographics between the two groups, the heavy smoking (+) group had a higher proportion of male sex (98.8% vs. 76.7%) and were older compared to the heavy smoking (-) group. Regarding the tumor status, no differences were observed between the two groups in terms of the number of tumor masses, maximal tumor size, and the presence of vascular invasion. AFP levels did not differ between the two groups. Both groups had a higher proportion of Child-Pugh class A (heavy smoking (-): 93.1% vs. (+): 91.3%, p = 0.496), and no statistical differences were noted in the treatment modalities between the two groups (p = 0.527).

3-year overall survival of heavy smoker

During the 3-year follow-up period of the study cohort, 393 patients were lost to follow-up, and 1531 patients were followed up until the end of the 3-year study period. A total of 282 mortality cases were documented in the study population, resulting in 1-, 2-, and 3-year survival rates of 95.0% (95% CI: 94.1, 96.0%), 89.2% (95% CI: 87.8, 90.6%), and 83.2% (95% CI: 81.4, 85.1%), respectively. Patients were categorized into four groups based on pack-years of smoking: non-smokers, light smokers, moderate smokers, and heavy smokers, and the 3-year OS was compared among these groups. Figure 2A depicts the Kaplan-Meier curves of these four groups. Overall, the four groups showed a significant difference in the 3-year OS (p = 0.008). When comparing the three smoking groups to the non-smoking group, light and moderate smokers did not differ significantly (p = 0.777 and 0.539, respectively). However, heavy smokers exhibited lower 1-, 2-, and 3-year survival rates of 91.2%, 85.5%, and 77.1%, respectively.
respectively, than the non-smoking group (1-, 2-, and 3-year survival rates of 96.0%, 90.4%, and 83.3%, respectively), with a significant difference observed in the 3-year OS (p = 0.016).

Since heavy smokers exhibited poorer outcomes compared to the other groups, the study population was further categorized into two groups: heavy smoking (+) group (≥ 40 pack-years) and heavy smoking (−) group (< 40 pack-years). In the heavy smoker cohort, 53 mortality cases were recorded, predominantly due to HCC, with a frequency of 38 occurrences, followed by complications resulting from liver cirrhosis (n = 3), other malignancies (n = 2), infections (n = 2), alcohol intoxication (n = 2), trauma (n = 2), cardiovascular diseases (n = 2), and cases with an undetermined etiology (Supplementary Figure 1). Figure 2B depicts the Kaplan-Meier curve comparing the survival rates of these two groups over a 3-year timeframe. The heavy smoking (−) group demonstrated a significantly higher 3-year OS rate than the heavy smoking (+) group (P = 0.011). Furthermore, the RMST and RMTL scores were compared between the two groups. The RMST was 31.92 and 33.36 months for the heavy smoking (+) and heavy smoking (−) groups, respectively, showing a significant difference between the two groups (−1.44, 95% CI: −2.87, −0.01, p = 0.048). The RMTL was 4.08 and 2.64 months for the heavy smoking (+) group and heavy smoking (−) group, respectively, demonstrating statistical significance in terms of the ratio of RMTL for the two groups (1.55, 95% CI: 1.07, 2.23, p = 0.019).

**Smoking cumulative dose-dependent survival risk**

The dose-dependent survival risk associated with smoking was assessed to further investigate the effects of heavy smoking on survival rates for patients with HCC. The HR for the 3-year OS based on the cumulative dose of smoking are shown in Figure 3. In the overall linear association, the HR was 1.002 for each pack-year smoked. In the restricted cubic spline model, the HR exceeded 1.0 at 20 pack-years and continued to rise until 40 pack-years, showing
Factors associated with 3-year overall survival

Univariate and multivariate analyses were conducted using the Cox proportional hazard model to determine the factors associated with the 3-year OS in the study cohort (Table 2). In the univariate analysis, heavy smoking, age ≥ 60 y, underlying cirrhosis, NAFLD as the cause of HCC, AFP level exceeding 200 ng/mL, tumor size > 3 cm, presence of vascular invasion, and Child-Pugh class A were all found to be associated with the 3-year OS. In the multivariate analysis, heavy smoking (HR 1.443, 95% CI: 1.006, 2.069, p = 0.046), age ≥ 60 y (HR 1.290, 95% CI: 1.000, 1.664, p = 0.050), underlying cirrhosis (HR 1.406, 95% CI 1.091, 1.812, p = 0.008), tumor size > 3 cm (HR 1.871, 95% CI: 1.462, 2.396, p < 0.001), presence of vascular invasion (HR 2.406, 95% CI: 1.653, 3.502, p < 0.001), and Child-Pugh class A (HR 0.353, 95% CI: 0.255, 0.490, p < 0.001) were identified as factors associated with the 3-year OS in the study population. In the multivariable stratified Cox regression analysis, heavy smoking was revealed to be a significant factor in the alcohol etiology (HR 1.769, 95% CI 1.113, 2.810, p = 0.016), male (HR 1.528, 95% CI 1.067, 2.190, p = 0.021), and age≥60 (HR 1.510, 95% CI 1.019, 2.236, p = 0.040) subgroups (Supplementary Figure 2).

Subgroup analysis on patients with suitable tumor burden for curative treatment

Subgroup analysis was conducted on selected patients who were generally deemed suitable for curative treatment, including RFA and surgical resection. Specifically, patients with a tumor size of < 3 cm (n = 1207), patients not presenting vascular invasion (n = 1827), and patients meeting the Milan criteria (n = 1491) were evaluated in the subgroup analysis. Figure 4 illustrates the Kaplan-Meier curves of these subgroups. In the subgroup of patients with tumor size < 3 cm, the heavy smoking (+) group exhibited 1-, 2-, and 3-year survival rates of 91.2%, 82.1%, and 75.6% respectively.
87.9%, and 78.3%, respectively, while the heavy smoking (−) group showed rates of 97.4%, 92.9%, and 87.2%, respectively, indicating inferior outcomes for the heavy smoking (+) group in terms of the 3-year OS (p = 0.005) (Figure 4A). Similarly, in the vascular invasion (−) group, heavy smoking was associated with worse outcomes in terms of the 3-year OS (p = 0.002), with a lower 3-year survival rate (77.0%) compared to that of the heavy smoking (−) group (85.1%) (Figure 4B). For patients meeting the Milan criteria, the heavy smoking (+) group demonstrated 1-, 2-, and 3-year survival rates of 93.4%, 88.4%, and 80.1%, respectively, while the smoking (−) group showed rates of 97.1%, 92.7%, and 87.6%, respectively, indicating a poor outcome for the heavy smoking (+) group in terms of the 3-year OS (p = 0.007) (Figure 4C).

Discussion

With the recent advancements in the landscape of advanced HCC treatment, there is a renewed focus on managing early stage HCC, which has become a primary concern for physicians. In this study, we investigated the association between the prognosis of HCC following curative treatments and cigarette smoking in a dose-dependent manner. Our analysis revealed that patients with HCC with a smoking history of > 40 pack-years exhibited significantly poorer outcomes in terms of the 3-year OS following curative treatment, including RFA or liver resection. Subgroup analysis of patients who were considered eligible for curative treatment in a real-world setting consistently demonstrated this adverse trend, indicating a worse 3-year OS among heavy smokers. Furthermore, our study identified heavy smoking as an independent factor contributing to a poor prognosis. To the best of our knowledge, this is the first study to elucidate the effect of heavy smoking on the prognosis of HCC following
Several studies have sought to reveal the correlation between smoking and HCC, with the majority indicating unfavorable outcomes. Concerning the HCC incidence, a large prospective study conducted in the US demonstrated an HR of 1.86 for HCC incidence among current smokers. Similar findings were observed in a study conducted in Korea, which revealed a heightened risk of HCC incidence among current smokers within the context of patients with metabolic dysfunction-associated fatty liver disease. Furthermore, several previous studies have highlighted the association between smoking and increased HCC mortality, which is consistent with the findings of our study. Lv et al. reported analogous results to our own, demonstrating that smoking escalates the risk of early morbidity including bile leakage and liver failure, following hepatic resection in HCC patients. Our study corroborates the findings of the aforementioned studies and offers additional meticulous analyses of the dose-dependent risk of smoking on early mortality in a nationwide cohort.

The most interesting aspect of our study was that, through a detailed analysis, we found smoking was a significant predictor of survival in patients who received curative treatment. This observation remained consistent even within a subgroup typically associated with favorable outcomes. The association between HCC and smoking could be attributed to several factors. First, the carcinogenic substances present in smoke, such as tar and vinyl chloride, can directly induce liver carcinogenesis. Our study's findings, particularly the association between heavy smoking and poor outcomes, may be partially supported by the direct oncogenic effects of these chemicals, as cumulative exposure to these chemicals could increase the risk of carcinogenesis. Additionally, evidence from a study conducted in Italy indicated that workers exposed to vinyl chloride exhibited increased mortality rates due to liver cirrhosis and
HCC, providing further support for our findings. Secondly, there may be a synergistic effect between smoking and other established risk factors for HCC. A meta-analysis of prospective studies suggested the presence of an interaction on the additive scale between smoking and hepatitis B virus, as well as multiplicative interactions between smoking and hepatitis C virus in terms of HCC development. Moreover, Wong et al. demonstrated the role of smoking in enhancing HBV viral load and liver inflammation, further supporting the synergistic relationship between smoking and these viral factors in HCC prognosis. Lastly, smoking also impairs the immune system. Moreover, smoking has been linked to chronic inflammation through genetic alterations. This impairment or imbalance in the immune system can make individuals more susceptible to infection, thereby leading to unfavorable outcomes in terms of survival rates among patients with cancer.

This study has several limitations. First, its retrospective design may have provided inaccurate information regarding the demographic characteristics of the study cohort. Specifically, smoking history was obtained from medical records through a simple questionnaire administered during appointments, introducing the possibility of recall bias regarding the cumulative dose of smoking. Additionally, the database lacked information on the date of HCC recurrence, thus limiting the comprehensive investigation of recurrence-free survival in our analysis. Finally, our study provides a relatively short timeframe for the analysis of patients with HCC undergoing curative treatments. Given that the anticipated survival of individuals with HCC receiving curative treatment surpasses five years, conducting additional studies with an extended follow-up period could more comprehensively elucidate the association between smoking and HCC survival. Despite these limitations, our study used hospital-based data representative of a nationwide cohort, thereby bolstering the robustness of
the findings. Therefore, the results of our study offer valuable insights into the role of smoking in this population. Our study also employed two novel statistical measures: RMST and RMTL. These markers have been demonstrated to be valuable in elucidating survival outcomes, particularly in cohorts where mortality rates are anticipated to be low. Using these markers in our analysis, we were able to present more intuitive results.  

Patients with early stage HCC seek a complete disease cure because of the nuance of the term ‘curative treatment.’ While patients with early HCC undergoing curative treatments are generally considered to be at a low risk of early mortality, a certain proportion of these individuals suffer from such an event. Through our meticulous analysis, patients with heavy smoking were found to be more vulnerable to such events, demonstrating heavy smoking as an independent factor associated with poor prognosis concerning the 3-year OS in patients with HCC who underwent curative treatments, such as RFA and liver resection. This finding underscores the significance of smoking cessation in this population, thereby offering crucial evidence for clinicians to counsel patients about quitting cigarette smoking.

Conflicts of Interest
The authors declare no conflict of interest. The funders had no role in the study design, collection, analyses, interpretation of data, writing of the manuscript, or decision to publish the results.

Ethics Statement
This study was approved by the Institutional Review Board of the Catholic University of Korea (approval number: OC22ZIDI0160). Informed consent was not required because this research
was a retrospective study.

**Funding Statement**

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**Data Availability:** The original contributions presented in the study are included in the article/Supplemental Materials; Further inquiries can be directed to the corresponding author.

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**Author contributions**

Conceptualization: JL, JYC, SKL

Data analysis and interpretation: JL, SKL

Data collection: JL, SKL
Manuscript writing: JL, SKL
Methodology: JL, JYC, SKL
Study concept and design: JL, SKL
Supervision: JYC, SKL
Final approval of the version to be published: All authors.
References


Figure Legends

Figure 1. Flowchart of Patient Selection

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation.
Figure 2. Three-Year Survival of Study Populations depending on the Pack-Years of Smoking (A) Dose-dependent survival rate, (B) Comparison between non-heavy smokers and heavy smokers.

PY, pack-years; RMST, Restricted Mean Survival Time; RMTL, Restricted Mean Time Lost.
Figure 3. Smoking Dose-Response Curve of the Hazard Ratios for 3-year survival

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, pack-years.
Figure 4. Subgroup Analysis of 3-Year Survivals between Non-Heavy Smokers and Heavy Smokers (A) HCC size less than 3 cm, (B) HCC without vascular invasion, and (C) HCC within Milan Criteria.

HCC, hepatocellular carcinoma
Table

Table 1. Baseline characteristics of enrolled patients

<table>
<thead>
<tr>
<th></th>
<th>Total (n=1924)</th>
<th>Heavy smoking (+) (n=1763)</th>
<th>Heavy smoking (+) (n=161)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>1512 (78.6)</td>
<td>1353 (76.7)</td>
<td>159 (98.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>61.1±10.5</td>
<td>60.8±10.7</td>
<td>65.2±7.1</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>24.6±3.4</td>
<td>24.1±3.2</td>
<td>0.040</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>1016 (52.8)</td>
<td>969 (55.0)</td>
<td>47 (29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td>600 (31.2)</td>
<td>517 (29.3)</td>
<td>83 (51.6)</td>
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<tr>
<td>NAFLD</td>
<td>308 (16.0)</td>
<td>277 (15.7)</td>
<td>31 (19.3)</td>
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<tr>
<td>Cirrhosis</td>
<td>1088 (56.5)</td>
<td>1003 (56.9)</td>
<td>85 (52.8)</td>
<td>0.357</td>
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<td>Platelet (K/µL)</td>
<td>169.1±69.7</td>
<td>168.0±69.6</td>
<td>181.4±70.0</td>
<td>0.022</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>48.0±57.5</td>
<td>48.3±59.2</td>
<td>43.9±32.9</td>
<td>0.350</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>40.6±59.8</td>
<td>41.3±62.1</td>
<td>33.3±20.7</td>
<td>0.106</td>
</tr>
<tr>
<td>TB (mg/dL)</td>
<td>0.9±1.0</td>
<td>0.9±1.0</td>
<td>0.9±0.8</td>
<td>0.541</td>
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<tr>
<td>Albumin (mg/dL)</td>
<td>4.1±0.5</td>
<td>4.1±0.5</td>
<td>4.0±0.5</td>
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<td>PT (INR)</td>
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<td>1.1±0.2</td>
<td>1.1±0.1</td>
<td>0.114</td>
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<tr>
<td>Cr (mg/dL)</td>
<td>0.9±0.8</td>
<td>0.9±0.7</td>
<td>1.0±1.0</td>
<td>0.084</td>
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<tr>
<td>Na (mEq/L)</td>
<td>139.8±3.0</td>
<td>139.8±3.0</td>
<td>139.4±3.0</td>
<td>0.084</td>
</tr>
<tr>
<td>Single tumor mass</td>
<td>1673 (87.0)</td>
<td>1529 (86.7)</td>
<td>145 (90.1)</td>
<td>0.271</td>
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<tr>
<td>Maximal tumor size (mm)</td>
<td>34.6±28.8</td>
<td>34.5±28.4</td>
<td>38.6±32.4</td>
<td>0.067</td>
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<tr>
<td>Vascular invasion</td>
<td>97 (5.0)</td>
<td>91 (5.2)</td>
<td>14 (8.7)</td>
<td>0.496</td>
</tr>
<tr>
<td>AFP (ng/mL)</td>
<td>2397.3±26325.6</td>
<td>2557.3±27480.5</td>
<td>645.6±3104.9</td>
<td>0.378</td>
</tr>
<tr>
<td>Child-Pugh class A</td>
<td>1788 (92.9)</td>
<td>1641 (93.1)</td>
<td>147 (91.3)</td>
<td>0.496</td>
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<td>MELD score</td>
<td>822±26</td>
<td>8.2±2.6</td>
<td>8.3±2.8</td>
<td>0.691</td>
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<td>Treatment</td>
<td></td>
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<td>RFA</td>
<td>586 (30.5)</td>
<td>541 (30.7)</td>
<td>45 (28.0)</td>
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<td>Surgical resection</td>
<td>1338 (69.5)</td>
<td>1222 (69.3)</td>
<td>116 (72.0)</td>
<td></td>
</tr>
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</table>

Values are presented as mean±standard deviation or number (%). Abbreviations: AFP, alpha fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; Cr, creatinine; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; RFA, radiofrequency ablation; TB, total bilirubin; PT, prothrombin time; AFP, alpha fetoprotein.
Table 2. Univariate and multivariate analysis of factors influencing 3-year survival

<table>
<thead>
<tr>
<th></th>
<th>3-year survival</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td></td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Heavy smoking (≥40PY)</td>
<td>1.573 (1.104, 2.241)</td>
<td>0.012</td>
<td>1.443 (1.006, 2.069)</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>1.289 (0.950, 1.750)</td>
<td>0.104</td>
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<tr>
<td>Age≥60</td>
<td>1.389 (1.091, 1.768)</td>
<td>0.008</td>
<td>1.290 (1.000, 1.664)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.965 (0.931, 1.001)</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1.349 (1.059, 1.718)</td>
<td>0.015</td>
<td>1.406 (1.091, 1.812)</td>
</tr>
<tr>
<td>Etiology - NAFLD (vs. others)</td>
<td>1.365 (1.021, 1.825)</td>
<td>0.036</td>
<td>1.179 (0.869, 1.600)</td>
</tr>
<tr>
<td>Platelet&lt;150K/µL</td>
<td>1.132 (0.896, 1.432)</td>
<td>0.299</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.054 (0.938, 1.185)</td>
<td>0.375</td>
<td></td>
</tr>
<tr>
<td>AFP&gt;200ng/mL</td>
<td>1.529 (1.151, 2.030)</td>
<td>0.003</td>
<td>1.295 (0.965, 1.736)</td>
</tr>
<tr>
<td>Tumor size&gt;3cm</td>
<td>1.886 (1.493, 2.382)</td>
<td>&lt;0.001</td>
<td>1.871 (1.462, 2.396)</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>3.113 (2.175, 4.456)</td>
<td>&lt;0.001</td>
<td>2.406 (1.653, 3.502)</td>
</tr>
<tr>
<td>Tumor number≥2</td>
<td>1.348 (0.983, 1.849)</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>Child Pugh Class A</td>
<td>0.318 (0.232, 0.437)</td>
<td>&lt;0.001</td>
<td>0.353 (0.255, 0.490)</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index; CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease; PY, pack-years.
Supplementary Materials

Supplementary Figure 1. Causes of Mortality among Heavy Smokers

Causes of Mortality Among Heavy Smokers

- 38 HCC
- 3 Complications of liver cirrhosis
- 2 Other malignancies
- 2 Infection
- 2 Cardiovascular disease
- 2 Alcohol intoxication
- 2 Trauma
- 2 Unknown cause

Total=53
Supplementary Figure 2. Hazard Ratio of Heavy Smoking for 3-Year overall survival using Multivariate Stratified Cox Proportional Hazards Model Analysis

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.77 (1.11, 2.81)</td>
<td>0.262</td>
</tr>
<tr>
<td>non-alcohol</td>
<td>1.16 (0.65, 2.08)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.53 (1.07, 2.19)</td>
<td>0.373</td>
</tr>
<tr>
<td>Female</td>
<td>0.01 (0.00, Inf)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1.51 (1.02, 2.24)</td>
<td>0.703</td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.25 (0.51, 3.07)</td>
<td></td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.57 (0.87, 2.85)</td>
<td>0.996</td>
</tr>
<tr>
<td>non-obese</td>
<td>1.57 (1.01, 2.44)</td>
<td></td>
</tr>
</tbody>
</table>