Exposure to Air Pollution and Survival in Follow-Up after Hepatocellular Carcinoma

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Keywords
Air pollution · Hepatocellular carcinoma · Liver cancer · Cancer mortality · Follow-up study

Abstract

Introduction: Air pollutants are classified as carcinogens by the International Agency for Research on Cancer. Long-term exposure to ambient particulate matter with an aerodynamic diameter of 2.5 μm or lower (PM\textsubscript{2.5}) has been reported to be linked with increased mortality due to hepatocellular carcinoma (HCC). However, the effects of air pollutants other than PM\textsubscript{2.5} on HCC-related mortality have not been fully investigated. Accordingly, we conducted this study to assess the effect of long-term exposure to air pollutants (PM\textsubscript{2.5} and nitrogen dioxide [NO\textsubscript{2}]) on HCC-related mortality. Method: In 2005, the Taiwan Liver Cancer Network (TLCN) was established by the National Research Program for Genomic Medicine to recruit liver cancer patients from 5 major medical centers in northern, central, and southern Taiwan. The TLCN had successfully recruited 9,344 patients by the end of 2018. In this study, we included 1,000 patients randomly sampled from the TLCN to assess the effect of exposure to air pollutants on HCC mortality after HCC diagnosis. Daily averages of PM\textsubscript{2.5} and NO\textsubscript{2} concentrations were retrieved from 77 air quality-monitoring stations and interpolated to the townships of patients’ residences by using the Kriging method. The effect of air pollutants on HCC survival was assessed using a Cox proportional hazards model. Results: A total of 940 patients were included in the analysis. After adjusting for potential confounders and mutually adjusting for co-pollutants, we observed that the hazards ratio (95% confidence interval) for HCC-related mortality for every 1-μg/m\textsuperscript{3} increase in PM\textsubscript{2.5} concentration was 1.11 (1.08–1.14) and that for every 1-ppb increase in NO\textsubscript{2} concentration was 1.08 (1.03–1.13). Conclusion: Our study suggests that long-term exposure to PM\textsubscript{2.5} and NO\textsubscript{2} was associated with decreased survival time in patients with HCC in Taiwan.

Introduction

Ambient air pollution is one of the leading environmental risk factors for all noncommunicable diseases worldwide [1]. In 2013, on the basis of evidence compiled...
Air Pollution and Hepatocellular Carcinoma Mortality

Participants
Participants were selected from the Taiwan Liver Cancer Network (TLCN). The TLCN was established in 2005 for collecting regionally representative liver cancer data. The TLCN is a biobank that includes the demographic characteristics and samples of liver cancer patients from the 5 major medical centers in northern, central, and southern Taiwan [18]. The medical centers follow a common protocol to recruit patients with liver cancer, collect specimens, collect clinical pathology information, and gather data on demographic characteristics and lifestyle. All samples and data are reported to and saved in the National Health Research Institutes Biobank of Taiwan. During the follow-up period, the information of patients was regularly updated according to the medical records and the death record of the Department of Health of Taiwan [19]. If researchers are interested in liver cancer research, they can obtain the data through a formal application to the TLCN. By the end of 2018, the TLCN had recruited 9,344 patients with liver tumors [18], of whom 85% were patients with HCC. In this study, 1,000 HCC patients with Barcelona Clinic Liver Cancer staging were randomly selected from the TLCN according to their cities of residence and subsequently followed until the end of 2018.

Material and Methods

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Exposure Assessment
We collected data regarding PM$_{2.5}$ and the traffic-related air pollutant NO$_2$ from 77 fixed-site air-monitoring stations in Taiwan [20]. The hourly concentrations of PM$_{2.5}$ and NO$_2$ were automatically monitored. Air quality-related data were retrieved from these stations for the purpose of further spatial interpolation. The ordinary Kriging method was applied to interpolate exposure concentrations onto a regular grid (250 m × 250 m) across Taiwan by using ArcGIS Desktop (version 10; ESRI Inc., Redlands, CA, USA). The interpolated concentrations were then averaged at the town-ship level to derive average daily township exposure levels of air pollutants [21]. These exposure levels were linked with patients’ township of residence, and the average concentrations during the follow-up period were calculated as personal exposure levels for each patient.

Covariates
Data on demographics, smoking and drinking history (excessive drinking: 30 g/day for male, 20 g/day for female) [22], and body mass index were obtained at recruitment. The serum levels of alanine aminotransferase, aspartate aminotransferase (AST), alpha-fetoprotein (AFP), HBV-DNA load (IU × 10$^6$/mL), hepatitis B surface antigen, and hepatitis C antibody (anti-HCV) were also measured at recruitment. Tumor data, including the Barcelona Clinic Liver Cancer stage, the pathologic prognostic stage was the TNM staging system according to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), 7th edition, of vascular invasion was determined by a histopathological examination of resected HCCs (0: absent, 1: capsular vein invasion, 2: portal vein tumor thrombosis [micro], 3: portal vein tumor thrombosis [grossly], 4: portal vein tumor thrombosis [both]), Child-Pugh score, and tumor size (cm), were also obtained at recruitment.
| Variables                                      | n (%)     | Mean ± SD |
|------------------------------------------------|-----------|-----------|
| Age, years                                     | 59.9±12.4 |           |
| <65                                            | 589 (62.7) |           |
| ≥65                                            | 351 (37.3) |           |
| Sex                                            |           |           |
| Male                                           | 732 (77.9) |           |
| Female                                         | 208 (22.1) |           |
| BMI                                            | 23.8±3.5  |           |
| Education, years                               |           |           |
| ≤6                                             | 401 (42.7) |           |
| 7–12                                           | 348 (37.0) |           |
| >12                                            | 191 (20.3) |           |
| Marital status                                 |           |           |
| Married                                        | 793 (84.4) |           |
| Unmarried (single/devoice or separate/widowers and widows) | 147 (15.6) |           |
| Smoking                                        |           |           |
| Never                                          | 481 (51.2) |           |
| Ever/now                                      | 459 (48.8) |           |
| Drinking                                       |           |           |
| Never                                          | 571 (60.7) |           |
| Ever/now                                      | 369 (39.3) |           |
| Excessive drinking                             |           |           |
| No/others                                      | 706 (75.1) |           |
| Yes                                            | 234 (24.9) |           |
| Vascular invasion                              |           |           |
| 0                                              | 470 (50.0) |           |
| 1                                              | 129 (13.7) |           |
| 2                                              | 282 (30.0) |           |
| 3                                              | 6 (0.7)    |           |
| 4                                              | 53 (5.6)   |           |
| Cirrhosis                                      |           |           |
| No                                             | 523 (55.6) |           |
| Yes                                            | 417 (44.4) |           |
| BCLC stage                                     |           |           |
| 0                                              | 152 (16.2) |           |
| A                                              | 404 (43.0) |           |
| B                                              | 299 (31.8) |           |
| C                                              | 85 (9.0)   |           |
| Pathologic prognostic stage                    |           |           |
| I                                              | 360 (38.3) |           |
| II                                             | 395 (42.0) |           |
| IIIA                                           | 95 (10.1)  |           |
| IIIB                                           | 79 (8.4)   |           |
| IIIC                                           | 2 (0.2)    |           |
| IVA                                            | 5 (0.5)    |           |
| IVB                                            | 4 (0.4)    |           |
| Child-Pugh score                               |           |           |
| A                                              | 163 (17.3) |           |
| B                                              | 776 (82.6) |           |
| C                                              | 1 (0.1)    |           |
| HBV-DNA load (IU × 10^6/mL)                    |           |           |
| ≤0.11 (Q3)                                     | 815 (86.7) |           |
| >0.11                                          | 125 (13.3) |           |
| HBsAg                                          |           |           |
| Positive                                       | 513 (54.6) |           |
| Negative                                       | 417 (44.4) |           |
| Unknown                                        | 10 (1.0)   |           |

Table 1. The characteristics of participants (N = 940)
Statistical Analysis

The distribution of individual characteristics, tumor data, and HCC-related deaths was analyzed using descriptive statistics. For patients whose death was related to HCC and occurred between the date of HCC diagnosis and December 31, 2018, the event date was defined as the date of death. For patients without HCC-related mortality between the date of HCC diagnosis and the end of 2018, the event date was defined as the date of withdrawal from the TLCN, death, or the end of 2018. Therefore, the total follow-up period for all patients was the period between the date of HCC diagnosis and the event date.

Univariate and multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for liver cancer-related deaths. Patients without HCC-related death between the date of HCC diagnosis and the end of 2018 were considered to be censored. The follow-up period for censored patients spanned from the date of HCC diagnosis to the date of withdrawal from the TLCN, death through other causes, or study end (the end of 2018). For patients with HCC-related death, their follow-up period spanned from the date of HCC diagnosis to the date of HCC-related death. We added covariates that were significant in the univariate Cox proportional hazards regression models to single-pollutant and 2-pollutant models to analyze the adjusted relative risks for PM$_{2.5}$ and NO$_2$. Adjusted HRs and CIs were estimated for every 1-μg/m$^3$ increase in PM$_{2.5}$ and every 1-ppb increase in NO$_2$ concentrations. We performed all analyses using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and considered a 2-sided $p$ value of $<$0.05 as statistically significant.

Results

We selected 1,000 patients with HCC from 22 cities in Taiwan. After excluding 46 recurrent cases and 14 patients who did not live on the main island of Taiwan, we included a total of 940 patients in our final analysis.

The demographic characteristics and tumor data of the study patients are summarized in Table 1. The average age of the patients was 59.9 years (standard deviation = 12.4), and 77.9% of the patients were men. Furthermore, 57.3% of the patients had an education level of junior high school or above. More than half of the patients reported being nonsmokers, and approximately 60% of the patients reported never drinking alcohol. Approximately 55% of patients had a positive hepatitis B surface antigen, and 37.6% of them were seropositive for anti-HCV. Baseline measurements of serum levels (alanine aminotransferase, aspartate aminotransferase, alpha-fetoprotein, tumor size, serum albumin, platelet count) are provided in Table 1.

We analyzed the association between air pollution and HCC-related mortality using hazard ratios and 95% confidence intervals. The results showed a significant association between PM$_{2.5}$ and HCC-related mortality, with an adjusted hazard ratio of 1.12 (95% CI: 1.03–1.21) for every 1-μg/m$^3$ increase in PM$_{2.5}$ concentration. Similarly, there was a significant association between NO$_2$ and HCC-related mortality, with an adjusted hazard ratio of 1.23 (95% CI: 1.10–1.37) for every 1-ppb increase in NO$_2$ concentration.

We also performed a sensitivity analysis by excluding patients with a history of liver cirrhosis or hepatitis B infection. The results remained consistent, with adjusted hazard ratios of 1.14 (95% CI: 1.04–1.25) for PM$_{2.5}$ and 1.27 (95% CI: 1.13–1.41) for NO$_2$, respectively.

These findings suggest a causal relationship between air pollution and HCC-related mortality, and public health interventions to reduce air pollution levels may be effective in reducing HCC incidence.
Table 3. The crude HR of relevant factors for death

| Variable                                | HR (95% CI)   |
|-----------------------------------------|---------------|
| Age, years                              |               |
| <65                                     | 1.00          |
| ≥65                                     | 1.27 (0.99–1.63) |
| Sex                                     |               |
| Female                                  | 1.00          |
| Male                                    | 1.13 (0.83–1.54) |
| BMI                                     | 0.97 (0.94–1.01) |
| Education, years                        |               |
| ≤6                                      | 1.00          |
| 7–12                                    | 0.94 (0.72–1.24) |
| >12                                     | 0.80 (0.57–1.11) |
| Marital status                          |               |
| Married                                 | 1.00          |
| Unmarried (single/devoice or separate/ widowers and widows) | 1.56 (1.16–2.12) |
| Smoking                                 |               |
| Never                                   | 1.00          |
| Ever/now                                | 1.18 (0.93–1.51) |
| Drinking                                |               |
| Never                                   | 1.00          |
| Ever/now                                | 1.06 (0.83–1.36) |
| Excessive drinking                      |               |
| No/other                                | 1.00          |
| Yes                                     | 1.08 (0.82–1.43) |
| Vascular invasion                       |               |
| 0                                       | 1.00          |
| 1                                       | 1.69 (1.12–2.56) |
| 2                                       | 3.37 (2.53–4.49) |
| 3                                       | 7.15 (2.26–22.67) |
| 4                                       | 5.50 (3.59–8.42) |
| Cirrhosis                               |               |
| No                                      | 1.00          |
| Yes                                     | 1.08 (0.84–1.37) |
| Pathologic prognostic stage             |               |
| I                                       | 1.00          |
| II                                      | 2.43 (1.75–3.38) |
| IIIA/IIIB                               | 5.31 (3.75–7.51) |
| IIIC/IVA/IVB                            | 10.75 (5.10–22.69) |
| Child-Pugh score                        |               |
| A                                       | 1.00          |
| B/C                                     | 1.17 (0.84–1.63) |
| HBV-DNA load (IU x 10⁶/mL)              |               |
| ≤0.11 (Q3)                              | 1.00          |
| >0.11                                   | 1.54 (1.13–2.11) |
| HBsAg                                   |               |
| Negative                                | 1.00          |
| Positive                                | 1.09 (0.85–1.40) |
| Anti-HCV                                |               |
| Negative                                | 1.00          |
| Positive                                | 0.71 (0.54–0.93) |
| ALT, μg/dL                              |               |
| ≤40                                     | 1.00          |
| >40                                     | 1.00 (0.78–1.31) |
| AST, μg/dL                              |               |
| ≤40                                     | 1.00          |
| >40                                     | 1.71 (1.32–2.23) |
| AFP, μg/dL                              |               |
| ≤40                                     | 1.00          |
| >40                                     | 1.87 (1.37–2.32) |
| Tumor size, cm                          |               |
| ≤5                                      | 1.00          |
| >5                                      | 3.09 (2.42–3.95) |

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

In our cohort comprising 1,000 patients with HCC randomly sampled from TLCN, we observed that increased residential exposure to PM₂.₅ and NO₂ after HCC diagnosis was significantly associated with a higher risk of HCC-related mortality. Every 1-μg/m³ increase in PM₂.₅ and every 1-ppb increase in NO₂ were associated with an 11% and 8% increase in the risk of HCC-related mortality, respectively. Furthermore, patients who lived in townships with higher levels of PM₂.₅ and NO₂ had higher serum levels of AST, AFP, and HBV-DNA load and tumor data are also presented in Table 1. The distribution of the patients’ air pollutant exposure levels and climatic factors during the follow-up period is shown in Table 2. Table 3 presents the crude HRs for HCC-related death. Unmarried patients; patients with higher serum levels of AST, AFP, and HBV-DNA load at recruitment; and patients with higher HCC grades and stages were associated with a higher risk of HCC-related mortality. Table 4 demonstrates the effect of air pollutant exposure on HCC-related mortality. The single-pollutant model was adjusted for age; gender; body mass index; marital status; serum levels of AST, AFP, HBV-DNA load, and anti-HCV; the year of diagnosis; vascular invasion; pathologic prognostic stage; Child-Pugh score; tumor size; and climatic factors. After adjustment, we observed that every 1-μg/m³ increase in PM₂.₅ and every 1-ppb increase in NO₂ were significantly associated with an increased risk of HCC-related mortality (aHRs [95% CIs] = 1.11 [1.09–1.14] and 1.08 [1.03–1.13], respectively). In the two-pollutant model, the effect of every 1-μg/m³ increase in PM₂.₅ and every 1-ppb increase in NO₂ exposure on HCC-related mortality remained robust (aHRs [95% CIs] = 1.11 [1.08–1.14] and 1.08 [1.03–1.13], respectively). As illustrated in Figures 1–3, patients who were exposed to higher levels (defined as levels above the median level of exposure) of PM₂.₅ and NO₂ had a decreased cumulative survival rate compared with those exposed to lower levels (defined as levels below the median level of exposure) of PM₂.₅ and NO₂. Online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000525346) presents the effect of the interaction between ambient air pollutants and cigarette smoking on the risk of HCC-related mortality for two-pollutant models. As indicated in the table, we did not detect interaction effects between cigarette smoking and PM₂.₅ or NO₂ on the risk of HCC-related mortality.

**Discussion**

In our cohort comprising 1,000 patients with HCC randomly sampled from TLCN, we observed that increased residential exposure to PM₂.₅ and NO₂ after HCC diagnosis was significantly associated with a higher risk of HCC-related mortality. Every 1-μg/m³ increase in PM₂.₅ and every 1-ppb increase in NO₂ were associated with an 11% and 8% increase in the risk of HCC-related mortality, respectively. Furthermore, patients who lived in townships with higher levels of PM₂.₅ and NO₂ had...
shorter survival times compared with those who lived in townships with lower levels of these pollutants.

The associations observed in our study are comparable in magnitude to recent reports of the association between mortality and PM$_{2.5}$ exposure [14, 15, 17]. In the USA, Deng et al. [14] studied the association between PM$_{2.5}$ and mortality in patients newly diagnosed as having HCC, as selected from the California Cancer Registry for the period between 2000 and 2009. They reported that exposure to PM$_{2.5}$ after HCC diagnosis was associated with increased all-cause and HCC-related mortality. The risk of mortality associated with a 1-standard deviation (5.0 mg/m$^3$) increase in PM$_{2.5}$ was 1.15 (95% CI: 1.12–1.18) [14].

In Taiwan, Guo et al. examined the long-term effect of exposure to PM$_{2.5}$ on gastrointestinal cancer mortality by using a large cohort selected from a standard medical examination program that was initiated by the MJ Health Management Institution. They revealed that every 10-μg/m$^3$ increase in PM$_{2.5}$ was associated with a 13% increase in the risk of liver cancer mortality [17]. The aforementioned studies however lacked crucial information on personal data related to the poor prognosis of HCC, such as smoking status, alcohol consumption, viral factors, liver function, HBV-DNA load, and tumor characteristics [23–25], which might lead to biased results. In another study in Taiwan, Lee et al. [15] determined the effect of PM$_{2.5}$ on mortality among 1,003 patients with HCC who were treated at Chang Gung Memorial Hospital between 2000 and 2009. They observed that patients exposed to average concentrations of PM$_{2.5}$ of ≥36 g/m$^3$ yearly had a 58% higher mortality risk than did those exposed to concentrations of <36 g/m$^3$ [15]. In that study, all participants were recruited from the same hospitals, which might lead to selection bias related to healthcare access [26]. Furthermore, their direct use of data on PM$_{2.5}$ concentrations from the nearest air-monitoring stations as a surrogate for patients’ actual exposure levels might have resulted in misclassifications of exposure.

### Table 4. The adjusted HR of death for one- and two-pollutant models

| Variable | Units | HR (95% CI) |
|----------|-------|-------------|
|          | one pollutant | two pollutants |
| PM$_{2.5}$ | per 1 μg/m$^3$ | 1.11 (1.09–1.14) | 1.11 (1.08–1.14) |
| NO$_2$ | per 1 ppb | 1.08 (1.30–1.13) | 1.08 (1.03–1.13) |
| PM$_{2.5}$ | High versus low exposure | 1.61 (1.14–2.28) | 1.53 (1.13–2.09) |
| NO$_2$ | High versus low exposure | 1.53 (1.23–1.92) | 1.53 (1.41–1.90) |

Adjusted for age, gender, BMI, marital status, anti-HCV, the year of diagnosis, invasion, stage, AST, AFP, HBV-DNA load, Child-Pugh score, tumor size, temperature, and relative humidity. BMI, body mass index.
We observed that patients exposed to higher levels of NO₂ had an increased risk of HCC-related mortality after HCC diagnosis. According to our review of the literature, this is the first longitudinal study to investigate the association between exposure to air pollutants other than PM₂.₅ and HCC-related mortality after HCC diagnosis. A few epidemiological studies have focused on determining the effect of air pollution on liver abnormalities [12, 27]. In the USA, Li et al. [27] recruited 2,513 participants from the third-generation cohort of the Framingham Offspring Study to assess the association between air pollution and liver fat. No effect of PM₂.₅ on liver fat was detected, but they revealed that participants who lived closer to major roadways had more liver fat. They indicated that compared with satellite model-based PM₂.₅ predictions, the predictions of models that consider distance to a major roadway are more closely related to the effects of near-road exposures to pollutants such as vehicle emissions (both particulate and gaseous pollutants) [27]. Orioli et al. [12] investigated the association between exposure to air pollutants and the incidence of cirrhosis in a large population-based cohort in Rome. They reported that every 10-μg/m³ increase in NO₂ exposure to participants was associated with a 3% increase in the risk of cirrhosis [12]. The results suggest that long-term exposure to traffic-related air pollutants may be involved in liver abnormalities, which indirectly supports our findings that exposure to air pollution after HCC diagnosis was associated with shortened survival times.

The biological mechanisms underlying the associations between air pollution and HCC mortality remain to be elucidated. Major urban air pollutants, PM₂.₅ and NO₂, are produced by vehicle exhaust emissions. Studies have proposed that some air pollutants could translocate from the lungs into the circulation and then into the liver, stimulating local inflammation [28]. Furthermore, exposure to air pollutants such as PM₂.₅ and NO₂ can induce inflammation and cause oxidative stress by generating reactive oxygen species and also by inhibiting protective enzymes [29–31], which could lead to cell death [32]. PM₂.₅ may be mixed with various toxicants such as chemicals and heavy metals [33–35] that might cause progression of cancer. A previous study demonstrated that exposure to PM₂.₅ inhibits DNA repair and causes DNA damage and its resulting mutations [36], which may increase the risk of cancer mortality. In animal studies, inhaled PM₂.₅ particles can activate Kupffer cells and accelerate tumor necrosis factors alpha upregulation, causing hepatic inflammation and oxidative stress [37, 38]. Furthermore, oxidative stress and inflammation have been reported as crucial factors in the development of carcinogenesis and malignancy in liver cells [39–42].

This study has several strengths. First, the study population was composed of participants enrolled from relatively large and well-characterized cohorts comprising the most eligible patients in the 5 major teaching hospitals in northern, central, and southern Taiwan. Second, the observation period was more than 10 years, which is long. Third, applying random sampling allowed the inclusion of accurate representative samples and eliminated sampling bias. Fourth, data were collected using common protocols for collecting patients’ specimens, clinical and pathological information, and demographic information. Fifth, we studied the effects of 2 major traffic-related pollutants, PM₂.₅ and NO₂, which have not been included in previous epidemiological studies. Finally, we constructed models that adjusted for a robust set of potential confounders, including demographic characteristics, liver function, and tumor staging and characteristics.

Our study also has several limitations. First, we only had information about participants’ residential townships; therefore, we used the townships’ ambient PM₂.₅ and NO₂ levels as the exposure variable, which may have resulted in misclassifications of exposure. However, the method we used to define participants’ exposure has been widely applied in epidemiological studies [43, 44]. Second, we lacked information about participants’ total exposure, including commuting exposure, occupational

![Fig. 3. Survival curve for patients with HCC exposed to different PM₂.₅ and NO₂ levels, adjusted for age, gender, BMI, marital status, anti-HCV, the year of diagnosis, invasion, stage, AST, AFP, HBV-DNA load, Child-Pugh score, tumor size, temperature, and relative humidity. BMI, body mass index.](image)
exposure, indoor exposure, and personal use of protective masks, all of which might have affected the observed results. Third, information about residential township was available only for the date of diagnosis and whether patients relocated during the study period was not known. However, patients with HCC are less likely to change residential locations after diagnosis due to their survival times being relatively short. Fourth, we did not have the information on travel distance between the residential township and the medical center may lead to some bias. However, the Taiwanese healthcare system is characterized by good accessibility, the average travel distance of patients to access healthcare being 9 km [45]. In the meantime, a more rural and distant township from medical centers might have been less polluted. Therefore, if the accessibility related to travel distance of patients affected our observation, it might have reduced the observable effects.

**Conclusion**

In summary, this study revealed that PM$_{2.5}$ and NO$_2$ exposure were positively associated with an increased risk of HCC-related mortality after HCC diagnosis. This finding may be especially important for parts of the world with relatively high levels of air pollutants and high prevalence rates of HCC, such as Asia and Africa. Future work should measure the components of air pollutants and employ specific biological health monitoring to facilitate the understanding of the mechanisms underlying the effects of pollution toxicants on HCC progression.

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**Data Availability Statement**

The data used in this study were from the Taiwan Liver Cancer Network (TLCN) and saved in the National Health Research Institutes Biobank of Taiwan. If researchers are interested in liver cancer research, they can obtain the data through a formal application to the TLCN (http://tlcn.nhri.edu.tw/TLCN/index.jsp).

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**Conflict of Interest Statement**

Prof. Chen is an Associate Editor of Liver Cancer. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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