Increased risk of hepatocellular carcinoma in patients with traumatic liver injury

Real-world data from a nationwide population-based study

Yen-Ju Chen, MDa,b, Chih-Jung Shen, MDa,b, Shao-Hua Yu, MD, PhDac, Cheng-Li Lin, MScd, Hong-Mo Shih, MDa,b,e,∗

1. Introduction

The liver is the largest solid abdominal organ with a relatively fixed position, which makes it prone to injury.1,2 The most common mechanism of liver injury is blunt abdominal trauma, which is often caused by motor vehicle accidents, pedestrian accidents, and falls. A population-based retrospective study using data from the Bureau of National Health Insurance (BNHI) database in Taiwan revealed a liver trauma incidence rate of 13.9 per 100,000 individuals.3 Liver injuries account for approximately 5% of all trauma admissions and typically include

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We extracted data of patients with traumatic liver injury between 2000 and 2013 from Taiwan National Health Insurance Research Database (n=15,966) and those of age-, gender-, occupation-, and index year-matched individuals without traumatic liver injury from the general population (n=63,864). Cox proportional hazard models were employed to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC occurrence in the traumatic liver injury cohort compared with that in the comparison cohort.

Patients with traumatic liver injury had an increased HCC risk (adjusted HR 2.13, 95% CI 1.59–2.85); this increased risk was more pronounced within 1 year after injury (adjusted HR 8.84, 95% CI 4.29–18.2). After >1 year of injury, HCC risk remained 1.53-fold higher in patients with traumatic liver injury than in those without traumatic liver injury (95% CI 1.08–2.15).

People with traumatic liver injury demonstrate a high HCC risk, particularly within the first year of the injury.

Abbreviations: aHRS = Adjusted HRs, BNHI = Bureau of National Health Insurance, CIs = confidence intervals, HBV = hepatitis B virus, HCC = Hepatocellular carcinoma, HCV = hepatitis C virus, HRs = Hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NH1 = National Health Insurance, NHIRD = National Health Insurance Research Database.

Keywords: hepatocellular carcinoma, real-world data, risk management, traumatic liver injury

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concomitant injuries, which contribute significantly to mortality and morbidity.\[3]\n
Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide\[11]; moreover, it is the fifth and seventh most common cancer in men and women, respectively.\[5\] Its poor prognosis makes it the second leading cause of cancer mortality, after lung cancer; it is responsible for 8.2\% of cancer-related deaths.\[6\] A study analyzing GLOBOCAN data highlighted considerable global variations in HCC incidence, which is particularly high in the majority of East Asia and sub-Saharan Africa but lower (but increasing) in North America and the majority of Europe.\[7\]

HCC is a complex disease associated with multiple risk factors and cofactors.\[8,9]\ In 80–90\% of patients, HCC is preceded by cirrhosis. Moreover, the common causes of cirrhosis have been identified as key risk factors for HCC.\[10\] Of particular concern is chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. HBV is responsible for an estimated 50–80\% of HCC cases worldwide, whereas 10–25\% of cases may be due to HCV infection.\[11\] Recent report by Vincenza et al\[12\] found that HCV-associated cirrhosis would reduce the incidence of HCC after treatment with antiviral agents. Alcohol-related cirrhosis is the third most common cause of HCC.\[13\] Aflatoxins in food and occupational exposure chemicals such as vinyl chloride monomers, organic solvents, and chlorinated pesticides can cause hepatotoxicity and increase the risk of HCC.\[14\] Other risk factors for HCC include nonalcoholic fatty liver disease, chronic liver disease, diabetes,\[15\] and gall stones and cholecystectomy.\[16,17\] Chronic inflammation is a potential carcinogenic mechanism for several types of cancer, including HCC. With the high HBV and HCV prevalence, HCC is the fourth most common malignancy in Taiwan. The age-adjusted incidence rate has been increasing—from approximately 15 per 100,000 individuals in the 1980s to approximately 30 per 100,000 individuals in recent years.\[18\]

Cell proliferation, change of cytokines, and inflammatory process is present in most liver injury disease. However, the association between traumatic liver injury and HCC risk remains unclear. Therefore, in this study, we used data from Taiwan National Health Insurance (NHI) Research Database (NHIRD) to investigate the traumatic liver injury–HCC risk relationship.

2. Methods

2.1. Data source

Taiwan’s NHI program was launched in 1995. It covers more than 99\% of Taiwan residents, and their claims data are included in the NHIRD; the claims data include inpatient and outpatient records, diagnoses, prescriptions, investigation items, and treatment of each beneficiary. Hospitalization data were used in the current study. To protect patient privacy, all data were deidentified and encrypted. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to identify diagnoses. Our study was approved by the Research Ethics Committee at China Medical University and Hospital in Taiwan (CMUH-104-REC2-115-R3).

2.2. Study population

The date of traumatic liver injury diagnosis for each patient was defined as the index date. In total, 15,966 patients with traumatic liver injury (ICD-9-CM: 864) were diagnosed between January 1, 2000, and December 31, 2013 (case cohort). They were randomly matched with 63,864 individuals without traumatic liver injury (comparison cohort) in a 1:4 ratio by index year, gender, age, occupation, and urbanization level. To evaluate HCC risk in patients with or without traumatic liver injury, the ICD-9-CM codes of 155.0 and 155.2 were selected for the diagnosis. Patients aged <20 years or diagnosed as having cirrhosis (ICD-9-CM: 571.2, 571.3, and 571.6) or HCC before the index date were excluded.

Preexisting comorbidities identified at baseline comprised HBV (ICD-9-CM: 070.2, 070.3, and V02.61), HCV (ICD-9-CM: 070.41, 070.44, 070.51, 070.54, and V02.62), chronic liver diseases (ICD-9-CM: 571.4), and alcohol-related diseases (ICD-9-CM: 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0–571.3, 790.3, and V11.3). The end date of the follow-up period was the date on which the patient was diagnosed as having HCC, died, or withdrew from the NHIRD or was December 31, 2013.

2.3. Statistical analysis

In descriptive statistics, categorical and continuous variables are presented by numbers (percentages) and means± standard deviations to describe the case–comparison cohort distributions, respectively. The chi-square and Student t tests were performed to examine the case–comparison cohort differences in terms of categorical and continuous variables, respectively. Person-years were calculated from enrollment until death or final follow-up (December 31, 2013), whichever came first. HCC incidence rate was computed by dividing traumatic liver injury events by person-years (every 1000 person-years).

Hazard ratios (HRs) and their 95\% confidence intervals (CIs) were estimated using Cox proportional hazard models to evaluate the association between traumatic liver injury and HCC. Adjusted HRs (aHRs) were estimated using multivariate Cox proportional hazard models after adjustments for age, gender, occupation, urbanization level, and comorbidities, including HBV, HCV, and chronic liver disease. The association between traumatic liver injury and HCC, stratified by characteristics and comorbidity, was analyzed as well. Cumulative incidence curves of HCC in cohorts were plotted on the basis of the Kaplan–Meier method, and log-rank tests were performed to evaluate the differences between the cumulative incidence curves.

All statistical analyses were conducted using SAS (version 9.4; SAS Institute, Cary, NC). The Kaplan–Meier plot was drawn using R (version 3.6.1; The R Foundation, Vienna, Austria). Statistical significance was determined using a 2-tailed P value of <.05.

3. Results

3.1. Baseline characteristics

In both the case and comparison cohorts, 49.3\%, 27.8\%, and 23.0\% were aged ≤49, 50–64, and ≥65 years, respectively, with the average age of 38.4 years; 35.0\% and 65.0\% of the patients were female and male, respectively. In terms of the occupation, white-collar, blue-collar, and other occupations were respectively noted in 46.5\%, 40.4\%, and 13.1\% of the case cohort and in 57.1\%, 32.7\%, and 10.2\% of the comparison cohort. Regarding urbanization level, residence are urbanization levels 1, 2, 3, and 4 were, respectively, noted in 21.7\%, 30.9\%, 19.0\%, and 28.4\%
of the case cohort and in 29.8%, 30.6%, 18.8%, and 20.8% of the comparison cohort. The percentage of patients with chronic liver diseases, HCV, HBV, diabetes, and alcohol-related diseases in the case cohort were significantly different from those in the comparison cohort (all \(P < .001\); Table 1).

### 3.2. Traumatic liver injury–HCC relationship

The case cohort exhibited a significantly higher HCC risk than did the comparison cohort (aHR 2.13; 95% CI 1.59–2.85), with HCC incidence rates of 0.75 and 0.34 per 1000 person-years in the case and comparison cohorts, respectively (Table 2).

### 3.3. Stratified analysis of traumatic liver injury–hepatocellular carcinoma association at ≤1 year of follow-up

As summarized in Table 3, patients with traumatic liver injury had higher HCC risk within ≤1 year of follow-up than those individuals without traumatic liver injury (aHR 8.84, 95% CI 4.29–18.2). In women, HCC risk within ≤1 year of the traumatic liver injury was 6.92-fold higher in the case cohort than in the comparison cohort (95% CI 1.74–21.4), and in men, it was 10.1-fold higher in the case cohort than in the comparison cohort (95% CI 4.14–24.8). In patients aged 50–64 and ≥65 years, it was 9.74- and 8.26-fold higher in the case cohort than in the comparison cohort, respectively (95% CI 1.78–53.4 and 3.74–18.3, respectively). In white- and blue-collar patients, it was 13.6- and 6.99-fold higher in the case cohort than in the comparison cohort, respectively (95% CI 4.18–44.3 and 2.63–18.5, respectively). In patients with and without any comorbidities, it was 6.76- and 10.2-fold higher in the case cohort than in the comparison cohort, respectively (95% CI 3.78–27.4 and 2.35–19.5, respectively).

Figure 1 illustrates the cumulative incidence of HCC in patients with or individuals without traumatic liver injury at ≤1 year of follow-up. The cumulative incidence of HCC was higher among patients with traumatic liver injury than those without traumatic liver injury (Log-rank test \(P < .001\)).

### 3.4. Stratified analysis of traumatic liver injury–hepatocellular carcinoma association at >1 year of follow-up

In men, patients aged ≥65 years, and those living in level 2 urbanization areas, HCC risk after >1 year of the traumatic liver injury was 1.69-, 1.72-, and 2.59-fold higher in the case cohort.
than in the comparison cohort, respectively (95% CI 1.15–2.48, 1.15–2.57, and 1.46–1.59, respectively). Taken together, patients with traumatic liver injury had higher HCC risk after >1 year of follow-up than did individuals without traumatic liver injury (aHR 1.53, 95% CI 1.08–2.15, Table 4).

Figure 2 illustrates the cumulative incidence of HCC in patients with or individuals without traumatic liver injury after >1 year of follow-up. The cumulative incidence of HCC was higher in the traumatic liver injury group than those without traumatic liver injury during the study period (Log-rank test $P=.008$).

### 4. Discussion

The main finding of this nationwide population-based retrospective cohort study in Taiwan is that patients with traumatic liver injury demonstrated a higher HCC incidence than did individuals without traumatic liver injury. To the best of our knowledge, this is the first study using real-world data investigating the association between traumatic liver injury and HCC. An 8.84-fold higher HCC risk was observed in patients with traumatic liver injury over the follow-up period of ≤1 year. HCC risk remained elevated for the first 10 years after traumatic liver injury; in other words, over the follow-up period over 10 years, HCC incidence in patients with traumatic liver injury remained higher than that of the comparison cohort, but the gap was narrowed with time.

An association between malignancies and tissue damage has been observed in several organs. One such association is between corrosive injury and esophageal cancer. Esophageal neoplasms (both adenocarcinoma and squamous cell carcinoma) may develop as a late complication of caustic injury at a rate 1000 to 3000 times higher than that expected in other patients of similar age. The reported incidence ranges from 2% to 30%, at an interval of 1 to 3 decades after ingestion. Cancer is most commonly observed in areas of anatomic narrowing, and may be related to increased exposure to caustic substances.

In Asia, habitual betel nut chewing, in particular, is associated with the occurrence and development of oral potentially malignant disorders or oral or pharyngeal cancers and esophageal cancer.

Inflammation is the hallmark of chronic hepatitis of various etiologies, and is thought to be a major trigger for liver carcinogenesis. HBV, HCV, nonalcoholic steatohepatitis, and alcohol consumption all cause chronic inflammation of liver tissue. The normal liver stroma remains intact as a barrier, whereas the stroma rich in cancer-associated fibroblasts and tumor-associated immune cells would replace the normal liver stroma.

The persistence of the inflammatory stimuli or dysregulation of cell proliferation prevents complete wound-healing and causes non-resolving inflammation that may result in liver fibrosis, cirrhosis, and tumor growth. Besides, during regeneration, oxidative stress has been regarded as a disease-exacerbating factor of chronic liver disease and related to carcinogenesis. While tissue repairment from chronic inflammation, hepatocyte apoptosis produces reactive oxygen species, resulting in constant inflammatory and fibrotic changes, which are important factors in the development of HCC.

In this study, we found an increased risk...
Figure 1. Cumulative incidence comparison of hepatocellular carcinoma in patients with (dashed line) or individuals without (solid line) traumatic liver injury for the follow-up periods of ≤1 year.

Table 4
Incidence and hazard ratio of hepatocellular carcinoma in the case cohort compared with those in the comparison cohort at >1 year of follow-up.

| Variables                  | Yes Event | PY  | Rate   | No Event | PY  | Rate   | Crude HR (95% CI) | Adjusted HR* (95% CI) |
|----------------------------|-----------|-----|--------|----------|-----|--------|-------------------|-----------------------|
| All                        | 47        | 82,257 | 0.57   | 132      | 359,510 | 0.37   | 1.57 (1.12, 2.18)† | 1.53 (1.08, 2.15)†     |
| Gender                     |           |      |        |          |       |        |                   |                       |
| Female                     | 9         | 28,886 | 0.31   | 32       | 122,808 | 0.26   | 1.20 (0.57, 2.51)  | 1.09 (0.51, 2.33)     |
| Male                       | 38        | 53,372 | 0.71   | 100      | 236,702 | 0.42   | 1.70 (1.17, 2.47)† | 1.69 (1.15, 2.48)†     |
| Age, yr                    |           |      |        |          |       |        |                   |                       |
| <49                        | 2         | 42,549 | 0.05   | 9        | 177,854 | 0.05   | 0.94 (0.20, 4.37)  | 0.88 (0.19, 4.09)      |
| 50–64                      | 10        | 24,293 | 0.41   | 35       | 108,549 | 0.32   | 1.29 (0.64, 2.60)  | 0.19 (0.58, 2.43)      |
| ≥65                        | 35        | 15,417 | 2.27   | 88       | 73,108  | 1.20   | 1.91 (1.29, 2.82)† | 1.72 (1.15, 2.57)†     |
| Occupation                 |           |      |        |          |       |        |                   |                       |
| White collar               | 15        | 38,345 | 0.39   | 56       | 205,061 | 0.27   | 1.45 (0.82, 2.55)  | 1.57 (0.88, 2.80)      |
| Blue collar                | 26        | 33,467 | 0.78   | 65       | 118,816 | 0.55   | 1.43 (0.91, 2.25)  | 1.37 (0.86, 2.19)      |
| Others*                    | 6         | 10,445 | 0.57   | 11       | 35,634  | 0.31   | 1.86 (0.69, 5.04)  | 2.02 (0.71, 5.75)      |
| Urbanization level†        |           |      |        |          |       |        |                   |                       |
| 1 (highest)                | 6         | 17,884 | 0.34   | 26       | 108,083 | 0.24   | 1.41 (0.58, 3.42)  | 1.54 (0.62, 3.86)      |
| 2                          | 19        | 25,362 | 0.75   | 39       | 111,336 | 0.35   | 2.15 (1.25, 3.73)† | 2.59 (1.46, 4.59)†     |
| 3                          | 11        | 15,280 | 0.72   | 31       | 65,875  | 0.47   | 1.55 (0.78, 3.08)  | 1.46 (0.73, 2.92)      |
| 4 (lowest)                 | 11        | 23,731 | 0.46   | 36       | 74,217  | 0.49   | 0.96 (0.49, 1.88)  | 0.93 (0.46, 1.85)      |
| Comorbidity§               |           |      |        |          |       |        |                   |                       |
| No                         | 33        | 76,245 | 0.43   | 115      | 350,869 | 0.33   | 1.33 (0.90, 1.96)  | 1.44 (0.98, 2.14)      |
of developing HCC after traumatic liver injury. Traumatic liver injury was an acute event that subsequently triggers liver repair, and as we discussed earlier, this damage repair process may contribute to a pro-carcinogenic environment. This effect resulted in a significantly increased risk of developing HCC within 1 year of traumatic liver injury. After adjusting for covariates including comorbidities of chronic liver diseases, the risk of developing HCC in the traumatic liver injury group was 10.2 times higher than that in the general population. The HR was even higher than the subgroup with comorbidities of chronic liver diseases. This may be another evidence that traumatic liver injury is an independent risk factor for HCC.

The liver has a remarkable ability to regenerate its mass after injury. Cell proliferation is activated during regeneration. Molecular changes during liver regeneration that activate and cause proliferation of mature hepatocytes might favor both liver chronic liver diseases, the risk of developing HCC after traumatic liver injury was 8.84 times that of the group without traumatic liver injury. Subgroup analysis also showed that, in patients without comorbidities of

| Variables | Traumatic liver injury | | | | | | Yes | No | Crude HR (95% CI) | Adjusted HR* (95% CI) |
|-----------|------------------------|---|---|---|---|---|---|---|---|---|
| Event     | PY                     | Rate | Event | PY | Rate | Crude HR (95% CI) | Adjusted HR* (95% CI) |
| Yes       | 14                     | 6013 | 2.33 | 17 | 8641 | 1.97 | 1.19 (0.59, 2.42) | 1.80 (0.86, 3.79) |

PY, person-years; rate, incidence rate per 1000 person-years.
Crude HR, relative hazard ratio.
* Adjusted HR, multivariable analysis, including age, sex, occupation, urbanization level, and comorbidities.
† Urbanization level was categorized into 4 levels according to the population density of residential areas, with level 1 being the most urbanized and level 4 the least urbanized.
‡ Other occupations included primarily those who were retired, unemployed, or from low-income groups.
§ Individuals with any comorbidity of chronic liver disease, hepatitis C, hepatitis B, diabetes mellitus, and alcohol-related diseases were classified into the comorbidity group.
\( P < .05. \)
\( P < .01. \)

Figure 2. Cumulative incidence comparison of hepatocellular carcinoma in patients with (dashed line) or individuals without (solid line) traumatic liver injury for the follow-up periods of >1 year.
regeneration and tumor growth. Growth factors, such as hepatocyte growth factor, epidermal growth factor, and transforming growth factors alpha and beta, which play an essential role in liver regeneration, are associated with tumor growth. Changes in gene expression, molecules, and cytokines may explain the increased incidence of HCC after traumatic liver injury observed in this study.

Age could be risk factor for HCC. In this study, patients aged >50 years exhibited a higher incidence rate of HCC. In addition, we also observed a higher incidence of HCC in male patients. Compared with the comparison cohort, patients aged >50 years with traumatic liver injury exhibited a 9.74-fold higher HCC risk within 1 year of the injury. When the follow-up period was >1 year, a 1.72-fold HCC risk was still present in patients aged ≥65 years. Men exhibit a 4 to 8 times higher incidence of HCC than do women. This finding may be partly attributed to the cumulative result of other associated factors, such as the higher incidence of cirrhosis and the higher levels of smoking and alcohol intake in men. Tables 3 and 4 display data highlighting the increasing incidence of HCC in men and older individuals.

This study’s large research sample, of 15,966 patients with traumatic liver injury, and use of a database managed by the BNHI for reimbursement purposes are considerable strengths that support data reliability and validity. The population-based design and large sample size lend credibility to our findings. However, several limitations must be noted. First, the NHIRD does not include details of tobacco use, alcohol consumption, body mass index, socioeconomic status, or other lifestyle-related factors that may be potential confounders. Second, the NHIRD only contains records of patients who have ICD-9-CM code 864 after being diagnosed as having traumatic liver injury; however, this might underestimate the incidence of traumatic liver injury if coding is not performed accurately. Furthermore, the severity of traumatic liver injury could not be identified using ICD-9-CM codes. Finally, our results do not reveal the exact mechanism underlying the traumatic liver injury–HCC association. Despite these potential limitations, our data sufficiently achieved the purpose of the study. Nevertheless, future studies using prospective, randomized interventions addressing these limitations and aid in clarifying the causal relationship between traumatic liver injury and HCC are warranted.

5. Conclusion

On the basis of real-world data from a nationwide population database, we observed a relatively high HCC risk in people with traumatic liver injury. The risk was particularly high within the first year of the traumatic liver injury. Physicians should thus arrange regular follow-ups for such high-risk patients. Further research identifying the mechanism of HCC development after traumatic liver injury is warranted.

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Author contributions

Conceptualization, Yen-Ju Chen, Chih-Jung Shen, and Hong-Mo Shih; Formal analysis, Chih-Jung Shen and Cheng-Li Lin; Funding acquisition, Shao-Hua Yu and Hong-Mo Shih; Investigation, Yen-Ju Chen; Methodology, Hong-Mo Shih; Resources, Cheng-Li Lin and Hong-Mo Shih; Software, Cheng-Li Lin; Validation, Shao-Hua Yu and Hong-Mo Shih; Writing – original draft, Yen-Ju Chen and Chih-Jung Shen; Writing – review & editing, Shao-Hua Yu and Hong-Mo Shih.

Conceptualization: Yen-Ju Chen, Chih-Jung Shen, Hong-Mo Shih.

Formal analysis: Chih-Jung Shen, Cheng-Li Lin.

Funding acquisition: Shao-Hua Yu, Hong-Mo Shih.

Investigation: Yen-Ju Chen.

Methodology: Hong-Mo Shih.

Resources: Cheng-Li Lin.

Software: Cheng-Li Lin.

Validation: Shao-Hua Yu, Hong-Mo Shih.

Writing – original draft: Yen-Ju Chen, Chih-Jung Shen.

Writing – review & editing: Shao-Hua Yu, Hong-Mo Shih.

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