Liver Cirrhosis and Risk of Intracerebral Hemorrhage
A 9-Year Follow-Up Study

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Background and Purpose—The purpose of this study was to investigate the risk of future intracerebral hemorrhage development in patients with liver cirrhosis.

Methods—Data were collected from the National Health Insurance Research Database of Taiwan. The study cohort included 948 patients with liver cirrhosis diagnosed in 1999 and 9480 age- and sex-matched patients of the same year. All patients were tracked from their index visits for 9 years.

Results—Intracerebral hemorrhage developed in 1.3% of patients with liver cirrhosis and 1.0% of patients in the comparison cohort during the follow-up period. Log-rank test analysis showed no significant difference between the 2 cohorts (P=0.39). A stratified Cox proportional regression model showed an adjusted hazard ratio of 1.62 (95% CI, 0.85 to 3.10) for patients with liver cirrhosis to develop intracerebral hemorrhage compared with patients without liver cirrhosis.

Conclusions—Patients with liver cirrhosis had a similar intracerebral hemorrhage incidence rate but a trend of increased risk for intracerebral hemorrhage compared with the comparison cohort during the 9-year follow-up period. (Stroke. 2011;42:0000-0000.)

Key Words: epidemiology ■ intracerebral hemorrhage ■ liver cirrhosis

Hypertension, high alcohol intake, and old age are well-known independent risk factors for intracerebral hemorrhage (ICH).1,2 On the other hand, liver cirrhosis is frequently associated with hematologic complications, especially thrombocytopenia and coagulation disorders.3 The risk for development of ICH in patients with liver cirrhosis remains elusive. Only a few studies have proposed that liver cirrhosis is a risk factor for ICH.4–6 However, these studies were either case series or case–control methodologies. The purpose of this study was to investigate the risk of ICH in patients with liver cirrhosis using a nationwide administrative database.

Methods

Database

The National Health Insurance Research Database is a large computerized database released by the Bureau of National Health Insurance. The National Health Insurance Research Database is provided to the public in Taiwan for research purposes. This study used the Longitudinal Health Insurance Database 2005, which contains all the original claims data of 1 million beneficiaries randomly selected from 25.68 million individuals in the registry. Because confidentiality assurances were addressed by the Bureau of National Health Insurance,7 Institutional Review Board approval was waived.

Subjects

The study cohort comprised patients seeking outpatient care in 1999 and who received a diagnosis of liver cirrhosis, International Classification of Diseases, 9th Revision, Clinical Modification, code 571.2 or 571.5. We assigned their first visit for the diagnosis of liver cirrhosis as the index visit. To enhance diagnostic validity, we selected only patients who had ≥2 constant diagnoses of liver cirrhosis during January 1, 1999, to December 31, 1999, for the study group (n=1043). We excluded patients <20 years and those ≥80 years (n=16) and patients who had any diagnosis of intracranial hemorrhage, International Classification of Diseases, 9th Revision, Clinical Modification code 430 to 432 (n=7), or hepatocellular carcinoma (HCC), International Classification of Diseases, 9th Revision, Clinical Modification code 155.0 (n=72), in the index year. The resulting study cohort included 948 patients with liver cirrhosis.

Our comparison cohort was selected from the remaining patients with outpatient visits in the same year. Like with the study cohort, we excluded patients who had ever had a diagnosis of intracranial hemorrhage or HCC in the index year. We randomly selected 10 times the number (n=9480) of age- and sex-matched subjects as the comparison cohort. Each patient in both the study cohort and the comparison cohort was then individually tracked to the last medical visit up to 9 years from their index visit to identify all who had hospitalization due to ICH (International Classification of Diseases, 9th Revision, Clinical Modification code: 431) or HCC (International Classification of Diseases, 9th Revision, Clinical Modification code: 155.0) during this period. Subjects with probable antithrombotic-related ICH
(defined as daily use of aspirin, clopidogrel, ticlopidine, aspirin plus extended-release dipyridamole, cilostazol, or warfarin prescribed within 60 days before ICH) were identified.

**Statistics**

We calculated the 9-year ICH- and HCC-free survival rates using the Kaplan-Meier method and used the log-rank test to compare the survival distributions between the 2 cohorts. Stratified Cox proportional hazard regression models were performed to analyze the hazard ratios of each factor.

**Results**

The mean age was 52 years (SD, 13 years) and 66.6% in both cohorts were male. The proportions of hypertension (12.8% versus 9.4%, \(P=0.001\)), diabetes mellitus (14.9% versus 5.9%, \(P<0.001\)) and hyperlipidemia (8.1% versus 4.3%, \(P<0.001\)) were significantly higher in patients with liver cirrhosis than those in the comparison group. There was no significant difference in the proportion of ischemic stroke in the index year between the cirrhosis and the comparison cohorts (1.1% versus 1.2%, \(P=0.875\)).

During the 9-year follow-up period, 1.3% (12 of 948) of patients with liver cirrhosis and 1.0% (96 of 9480) of patients without liver cirrhosis developed ICH. Probable antithrombotic-related ICH was identified in 23 subjects (1 in the study cohort versus 22 in the control cohort). In contrast, 16.7% (158 of 948) of the patients with liver cirrhosis but only 0.8% (75 of 9480) of patients without liver cirrhosis had HCC during the same follow-up period.

The log-rank test showed no significant difference in the proportion of ischemic stroke in the index year between the cirrhosis and the comparison cohorts (1.1% versus 1.2%, \(P=0.875\)).

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The log-rank test showed no significant difference between patients with liver cirrhosis and the comparison cohort for the development of ICH (Figure A). However, as expected, patients with liver cirrhosis had significantly lower 9-year HCC-free survival rates compared with patients in the comparison group (\(P<0.001\), Figure B).

The crude hazard ratio for ICH during the 9-year follow-up period between the study and comparison cohorts was 1.30 (95% CI, 0.71 to 2.37; \(P=0.392\)). After adjusting for state of comorbid hypertension, diabetes, hyperlipidemia, ischemic stroke, and the stratified factors patient age, gender, and probable antithrombotic-related ICH, the hazard ratio for ICH for patients with liver cirrhosis was 1.62 (95% CI, 0.85 to 3.10; \(P=0.145\)) compared with patients in the comparison cohort. In contrast, the crude hazard ratio for development of HCC for patients with liver cirrhosis was 23.40 (95% CI, 17.77 to 30.81; \(P<0.001\)) compared with patients in the comparison cohort.

**Discussion**

This population-based 9-year follow-up study demonstrated that patients with liver cirrhosis had a similar rate (1.3% versus 1.0%) of ICH development compared with the comparison cohort.

One previous study showed that patients with liver cirrhosis and noncirrhotic alcoholic liver diseases had an increased ICH risk. The explanation for such a discrepancy between this study and the present study includes the differences in ethnicity, age distribution, and methodology. The strength of the present study is the population-based database as a research source and the follow-up study design. Moreover, the large sample size provided considerable statistical power to detect differences among the 2 cohorts.

However, this study has limitations. This database contained no actual information about alcohol consumption of individuals and the causes and the severity of liver cirrhosis. Therefore, there might not have been enough variables for the adjusted model.

**Conclusions**

Patients of Chinese ethnicity with liver cirrhosis had a similar ICH incidence rate but a trend of increased risk for ICH. Future studies are needed to clarify the association between ICH and liver diseases of different causes and grades of severity.
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Disclosures
None.

References
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