

Risk factors for stroke recurrence in patients with hemorrhagic stroke

Cheung-Ter Ong (✉ ctong98@yahoo.com.tw)

Ditmanson Medical Foundation Chiayi Christian Hospital

Yi-Sin Wong

Ditmanson Medical Foundation Chiayi Christian Hospital

Ching-Fang Tsai

Ditmanson Medical Foundation Chiayi Christian Hospital

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Abstract

Background

The risk factors for recurrence of hemorrhagic or ischemic stroke in patients with intracranial hemorrhage (ICH) are inconclusive. This study was designed to investigate the risk factors for stroke recurrence in patients with ICH.

Methods

This population-based case-cohort study analyzed the data obtained from a randomized sample of 2 million subjects in the Taiwan National Health Insurance Research Database. The survival of patients with hemorrhagic stroke from January 1, 2000 to December 31, 2013 was included in the study.

Results

During the 5-year follow-up period, the recurrence rate of stroke was 12.2% (6.88% hemorrhagic stroke, 5.24% ischemic stroke). The recurrence rate of stroke was 14.2% in the without antiplatelet group and 7.9% in the antiplatelet group. The risk factors for hemorrhagic stroke were age (odds ratio [OR], 2.48), hypertension (OR: 2.24), atrial fibrillation (OR: 1.87), cardiovascular disease (OR: 1.41), and ischemic stroke history (OR: 1.56). The risk factors for ischemic stroke were age (OR: 2.57), hypertension (OR: 2.23), atrial fibrillation (OR: 1.87), cardiovascular disease (OR: 1.42), and ischemic stroke history (OR: 1.6).

Conclusion

The risk factors of stroke recurrence were age, hypertension, atrial fibrillation, cardiovascular disease, and ischemic stroke history. Antiplatelet therapy may help prevent the recurrence of stroke.

Introduction

Though the incidence and mortality rates of stroke with intracranial hemorrhage declined gradually¹, hemorrhagic stroke still accounts for 10%–20% of patients with stroke²⁻⁴. The global burden of hemorrhagic stroke is gradually increasing. Risk factors for intracranial hemorrhage included hypertension and warfarin use⁵⁻⁷. The survival outcomes after hemorrhagic stroke include mortality, functional impairment, quality of life impairment, intracerebral hemorrhage recurrence, ischemic stroke, cognitive impairment, psychiatric diseases, and epilepsy⁸. The annual rate of stroke recurrence after intracranial hemorrhage was approximately 5%–10%^{9,10}. However, the report on the type of recurrent stroke after the patients with intracranial hemorrhage is inconclusive. Studies have reported that patients with intracranial hemorrhage have a higher risk of hemorrhage recurrence than those with ischemic stroke^{11,12}. Some studies have reported that patients with deep intracranial hemorrhage have a higher risk of ischemic stroke recurrence than those with hemorrhagic stroke and those with lobar hemorrhage

have an increased risk of hemorrhagic stroke recurrence¹⁰. However, some studies have found that the type of recurrent stroke was not significantly different between patients with lobar hemorrhage and those with deep hemorrhage stroke^{9, 13}. Murthy et al. have found that compared with individuals without intracerebral hemorrhages (ICH), patients with ICH have an increased risk of ischemic stroke with a hazard ratio (HR) of 3.1¹⁴.

A study has shown that inadequate blood pressure control increases the probability of ICH recurrence¹⁵. In patients with ICH who received antiplatelet drugs, the rate of ICH recurrence and hemorrhage volume did not increase^{16, 17}. In contrast, Biffi et al. have found that the use of antiplatelet drugs may increase the risk of ICH recurrence in patients with lobar hemorrhage¹⁵.

Stroke recurrence may increase mortality and impair daily activity and function. Presently, the risk factors for ischemic and hemorrhagic stroke recurrence remain inconclusive. Therefore, this study was designed to determine and investigate the risk factors for ischemic or hemorrhagic stroke recurrence in patients with intracranial hemorrhage in Taiwan.

Methods

Data source and ethics approval

This population-based case-cohort study used data from the Taiwan National Health Insurance Research Database (NHIRD) that comprises data obtained from 2 million individuals. The National Health Insurance (NHI) program in Taiwan has been operating since 1995. The NHIRD is a research database developed by the NHI Research Institute and contains patient healthcare data from hospitals, outpatient clinics, and community pharmacies. NHI encompasses more than 99% of 23 million individuals and 95% of the hospitals in Taiwan. The NHI Research Institute provides the database to researchers after anonymizing all personal information. This study included data retrieved from the “Longitudinal Health Insurance Database” (LHID 2005) from a random sample of 2 million individuals within the NHIRD, with linked longitudinal data available from 2000 to 2013. The randomized data (LHID 2005) represent all beneficiaries as no significant differences in sex, age, and premium rate are found between individuals in the LHID 2005 and the original NHIRD datasets. The codes of the International Classification of Diseases, Ninth Revision (ICD-9) were used to define diseases. This study was approved by the Institutional Review Board of Ditmanson Medical Foundation Chiayi Christian Hospital, Taiwan (CYCH-IRB: 2020131).

Study subjects and definitions

Hemorrhagic stroke was defined as an episode of rapidly developing neurological deficit attributed to the focal collection of blood within the brain parenchyma or ventricular system (ICH) or due to subarachnoid bleeding (subarachnoid hemorrhage) not caused by trauma¹⁸. All hospitalized patients with the diagnosis of hemorrhagic stroke (ICD-9 codes: 430 and 431) between January 1, 2000 and December 31,

2013 were included in the study. The exclusion criteria were as follows: 1) patients younger than 20 years; 2) those who had a history of hemorrhagic stroke; 3) those who continue to use antiplatelet drugs for more than 7 days 1 month before the onset of hemorrhagic stroke; 4) those with stroke recurrence within 1 month before hemorrhagic stroke onset; and 5) those who died within 1 month after stroke onset.

In total, 12,053 patients were hospitalized under the discharge diagnosis of hemorrhagic stroke. Among them, 75 patients were younger than 20 years, 1,876 patients used antiplatelet drugs for more than 7 days within 1 month before stroke onset, 153 patients had stroke recurrence within 1 month after stroke onset, and 2,902 patients died within 1 month after stroke onset, all of whom were excluded from this study. Finally, 7,589 patients were included in the study (Figure 1).

Separate propensity score matches were performed using a ratio of 1:2 to compare the risk of stroke recurrence between the groups with and without the use of antiplatelet drugs. All methods were performed in accordance with relevant guidelines and regulations.

Outcome measure

The primary endpoint of this study was new-onset hemorrhagic or ischemic stroke.

Statistical analysis

In this study, we compared the rate of stroke recurrence between patients who used antiplatelet drugs and those who did not receive antiplatelet drugs using propensity score matching with a ratio of 1:2 to match the study patients based on age, sex, and clinical comorbidity index (CCI). The baseline characteristics of the patients as categorical variables were compared using the chi-square test. Continuous variables were compared using the t-test. Cox proportional hazards regression models were used to evaluate the HRs and 95% confidence intervals (CIs) for the recurrence of ischemic and hemorrhagic stroke in each risk factor.

Results

From 2000 to 2013, 7,589 patients fulfilled the inclusion criteria for this study. After 1:2 propensity score matching for sex, age, and CCI, 6,180 patients were included in the analysis, including 4,120 patients in the without antiplatelet group and 2,060 patients in the antiplatelet group. The age, sex, and stroke severity and ischemic stroke history were not significantly different between the without antiplatelet and antiplatelet groups. The probability of admission to the intensive care unit (ICU) and hospitalization day longer than 9 days was higher the without antiplatelet group. The rates of diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, cardiovascular disease, and congestive heart failure were higher in the antiplatelet group (Table 1).

During the 5-year follow-up period, stroke in 751 patients recurred; the recurrence rate of stroke was 12.2% (751/6180), of whom 6.88% (426/6180) had hemorrhagic stroke and 5.24% (325/6218) had ischemic stroke. The rate of stroke recurrence was 14.2% (587/4120) in the without antiplatelet group and 7.9% (164/2060) in the antiplatelet group. Moreover, the rates of hemorrhagic and ischemic stroke recurrence were all lower in the antiplatelet group. The recurrence rates of hemorrhagic stroke were 7.89% and 4.9% in the without antiplatelet and antiplatelet groups ($p < 0.01$), while the recurrence rates of ischemic stroke were 6.36% and 3.06% ($p = 0.045$), respectively.

The risk factors for hemorrhagic stroke recurrence were age, hypertension, atrial fibrillation, cardiovascular disease, and ischemic stroke history. The HR of hemorrhagic stroke was 1.98 (95% CI, 1.13–3.58) in patients aged between 45 and 59 years and 2.48 (95% CI, 1.38–4.40) in patients aged ≥ 60 years. The HR of hemorrhagic stroke was 2.24 (95% CI, 1.27–3.93) in patients with hypertension, 1.87 (95% CI, 1.29–2.7) in patients with atrial fibrillation, 1.41 (95% CI, 1.14–1.76) in patients with cardiovascular disease, and 1.56 (95% CI, 1.06–2.29) in patients with a history of ischemic stroke. The antiplatelet group seemed to have a lower risk of hemorrhagic stroke with an HR of 0.86 (95% CI, 0.7–1.05); however, it did not reach statistical significance (Table 2).

The factors for ischemic stroke recurrence were age, hypertension, atrial fibrillation, cardiovascular disease, and history of ischemic stroke. The HR of ischemic stroke was 2.05 (95% CI, 1.14–3.7) in patients aged between 45 and 59 years and 2.57 (95% CI, 1.43–4.63) in patients aged ≥ 60 years. The HR of ischemic stroke was 2.23 (95% CI, 1.27–3.91) in patients with hypertension, 1.87 (95% CI, 1.3–2.7) in patients with atrial fibrillation, 1.42 (95% CI, 1.14–1.76) in patients with cardiovascular disease, and 1.6 (95% CI, 1.09–2.36) in patients with a history of ischemic stroke. The use of antiplatelet drugs seemed to have increased the risk of ischemic stroke with an HR of 1.17 (95% CI, 0.95–1.43); however, it did not reach statistical significance (Table 3).

Discussion

The main findings of this study include the following: 1) in patients with ICH stroke, the 5-year rate of stroke recurrence was 12.2%; 2) stroke recurrence was more frequent in patients with hemorrhagic stroke than that in patients with ischemic stroke with a ratio of 1.31; 3) antiplatelet therapy can decrease the risk of ischemic and hemorrhagic stroke recurrence.

Studies have shown that in patients with ICH stroke who were followed for less than 3–5 years, the rate of hemorrhagic stroke recurrence was between 7% and 12%. In a single-center study, with a mean follow-up period of less than 3.6 years, Hill et al. have found that the rate of hemorrhagic stroke recurrence was 8.72% (15/172)¹⁰. Bailey et al. have reviewed data with a mean follow-up of 3.4 person-year and found that the rate of hemorrhagic stroke recurrence was 8.35% (157/1880) and 2.4% per patient-year¹¹. In a study with a follow-up duration of less than 5 years, Vermeer has reported that the rate of hemorrhagic stroke recurrence was 12% (30/243) and the annual rate of ICH recurrence was 2.1%¹⁹. In this study, with a follow-up duration of less than 5 years, the rate of hemorrhagic stroke recurrence was 6.89%, which is

mildly lower than that reported in a previous study. The difference may be due to the stroke type. Studies have shown that patients with lobar hemorrhage have a higher risk of hemorrhage recurrence than those with deep hemorrhage^{9, 11, 12}. Vermeer has reported a higher rate of hemorrhagic stroke recurrence than this study; the difference may be related to the higher proportion (55%) of patients with lobar hemorrhage in Vermeer's study¹⁹.

The rate of ischemic stroke recurrence was 6.36% in patients who did not use antiplatelet drugs. The rate of ischemic stroke recurrence was close to that reported by Vermeer et al.¹⁹ but lower than that found in another study¹³. In a study with a 5-year follow-up period, Casolla et al. have found that the cumulative rate of ischemic stroke recurrence was 9.8%. The difference could be because the patients in this study was younger than those in Casolla et al.'s study (mean age, 62.2 years vs. 70 years, respectively), and this study included patients with subarachnoid hemorrhage. Moreover, patients with hemorrhagic stroke have a higher risk of ischemic stroke recurrence than those without stroke history. Murthy et al. have found that patients with a history of hemorrhagic stroke had a higher risk of ischemic stroke recurrence than those without hemorrhagic stroke history, with an HR of 3.1¹⁴.

Some studies have found that patients with hemorrhagic stroke have a higher risk of brain hemorrhage than those with ischemic stroke¹¹. However, some studies have found that ischemic stroke is more frequent than hemorrhagic stroke^{9, 10, 13}. Moreover, this study found that hemorrhagic stroke was more frequent than ischemic stroke. The difference may be related to patient characteristics and location of intracranial hemorrhage. Studies have found that patients with lobar hemorrhage have a higher risk of ICH recurrence, and deep hemorrhage increases the risk of ischemic stroke recurrence^{10, 20}. ICH is also a risk factor for ischemic stroke recurrence.

It is reasonable to consider that antiplatelet therapy may increase the risk of hemorrhage and decrease the risk of ischemic stroke. However, this study found that antiplatelet therapy not only decreased the risk of ischemic stroke but also decreased the risk of hemorrhagic stroke. The result agrees with those reported in a previous study. Murthy et al. have found that antiplatelet therapy did not affect mortality and clinical outcomes in patients with ICH²¹. The condition may be because most patients with hemorrhagic stroke have many stroke risk factors and patients who regularly used antiplatelet drugs have more aggressive blood pressure and blood sugar control (Table 1).

This study has several limitations. First, this was a retrospective study; we did not have data regarding deep hemorrhage or lobar hemorrhage. Second, stroke recurrence was based on the diagnosis of ischemic or hemorrhagic stroke among hospitalized patients, which may have underestimated the rate of stroke recurrence. Third, information on stroke risk control was unavailable, which may have affected the rate of stroke recurrence and stroke type.

In conclusion, the risk of stroke recurrence is high in patients with intracranial hemorrhage. Antiplatelet therapy did not increase risk of intracranial hemorrhage recurrence. For patients at a high risk of stroke or cardiovascular disease, antiplatelet therapy may prevent stroke recurrence.

Declarations

Acknowledgment

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Tables

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Figures

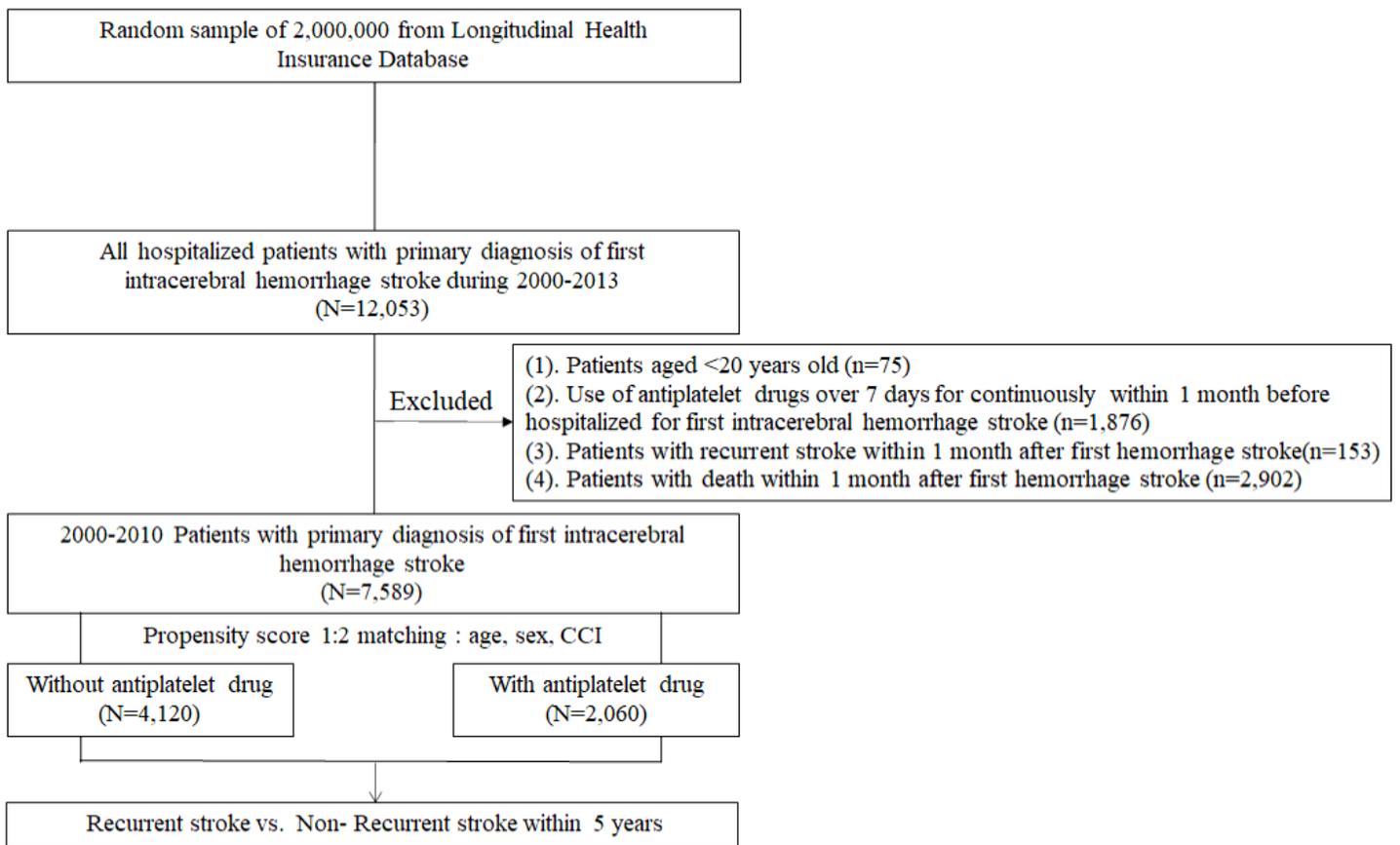


Figure 1

Flow chart of patient enrollment

CCI: clinical comorbidity index.

Supplementary Files

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