

Patients with Cerebral Stroke Have an Increased Risk of Gastroesophageal Reflux Disease: A Population-Based Cohort Study

Chen-Shu Chang, MD,^{*,†} Hsuan-Ju Chen, MS,^{‡,§} and Chun-Hui Liao, MD^{‡,||}

Background: Medical complications following stroke often result in significant morbidity. This study was designed to investigate the prevalence and risk of gastroesophageal reflux disease (GERD) between patients with stroke and those without stroke in Taiwan. **Methods and Results:** This retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database. The study included 18,412 patients newly diagnosed as having stroke during 2000–2006 and 18,412 patients without stroke frequency-matched by sex, age, and index year. All patients were followed from the index date to December 31, 2011. The Cox proportional hazards regression model was used to estimate the GERD risk. The GERD risk was approximately 1.51-times higher in the stroke group than in the nonstroke group, after adjustment for age, sex, and the cumulative incidence of some comorbidities. GERD was positively associated with stroke; the male sex (adjusted hazard ratio [HR] = 1.31); an age of 65 years or older (adjusted HR = 1.11); hyperlipidemia (adjusted HR = 1.14); ischemic heart disease (adjusted HR = 1.27); renal disease (adjusted HR = 1.45); and use of aspirin (adjusted HR = 2.34), clopidogrel (adjusted HR = 1.41), and dipyridamole (adjusted HR = 1.30). **Conclusions:** This study indicates a significantly higher GERD risk in patients with stroke than in the nonstroke group. In clinical practice, neurologists should focus on the risk of GERD symptoms. **Key Words:** Population-based study—stroke—gastroesophageal reflux disease—Taiwan.

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From the ^{*}Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan; [†]Department of Medical Laboratory Science and Biotechnology, Medical Imaging and Radiological Sciences, Central Taiwan University of Science and Technology, Taichung, Taiwan; [‡]College of Medicine, China Medical University, Taichung, Taiwan; [§]Management Office for Health Data; and ^{||}Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan.

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Address correspondence to Chun-Hui Liao, MD, Department of Psychiatry, China Medical University Hospital, No. 2, Yuh-Der Road, Taichung 404, Taiwan. E-mail: liau81@gmail.com.

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Introduction

Medical complications following stroke often result in significant morbidity and mortality.¹ Gastrointestinal complications can occur in nearly 50% of patients with stroke, but they have received less attention.^{2,3} These sequelae also contribute to an increased dependence on others, poor neurologic recovery, and even death after stroke.⁴

Gastroesophageal reflux disease (GERD), characterized by acid regurgitation or heartburn, severely affects quality of life, with troublesome complications.^{5,6} Multivariate analysis has revealed an increasing prevalence of GERD worldwide.^{7,8} A questionnaire study revealed a higher prevalence of GERD in patients with ischemic stroke than in the general population.⁹ The association between GERD and stroke has been inconsistent because of limited sample sizes or cross-sectional study designs. The present retrospective cohort study investigated the association between stroke and GERD by data from the National Health Insurance Research Database (NHIRD) (2000-2011), which has been a valuable data resource for many epidemiological studies in Taiwan.^{10,11}

Materials and Methods

Data Source

Taiwan's National Health Insurance Administration established the National Health Insurance program in March 1995. As of 2014, this program has provided health-care coverage to more than 99% of Taiwan's residents. In this study, we used the Longitudinal Health Insurance Database 2000 (LHID2000), which contains the claims data of 1 million beneficiaries randomly sampled from approximately 23.75 million insured individuals registered from 1996 to 2011. The NHIRD contains data on sex; birth date; ambulatory visit dates; admission and discharge dates; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes; and complete prescription details. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

Study Population

In this population-based study, we identified patients aged 20 years or older with newly diagnosed stroke (ICD-9-CM 430-438) using the hospital discharge diagnosis codes but without a history of GERD (ICD-9-CM 530.11 and 530.81) between 2000 and 2006 as the stroke group. The date of the first diagnosis of stroke was considered the index date. Furthermore, we divided the stroke group into 2 subgroups: hemorrhagic stroke (ICD-9-CM 430-432) and ischemic stroke (ICD-9-CM 433-438). For each patient with stroke, 1 insured individual without stroke and without a history of GERD was randomly selected and frequency-matched by sex, age (in 5-year intervals),

and index year; this group was identified as the nonstroke group.

Outcomes and Covariates

The primary outcome was GERD (ICD-9-CM 530.11 and 530.81) through record linkage with ambulatory and admission care data in the NHIRD. In the Taiwan National Health Insurance program, the prescription of proton pump inhibitor (PPI) was not allowed to be prescribed without the endoscopic diagnosis of GERD or peptic ulcer. To increase the validity of GERD diagnosis, we included only patients who were treated with PPIs after the diagnosis of GERD. All patients were followed from the index date to the study end point, namely GERD onset, withdrawal from the insurance system, or end of 2011.

Patients with a history of diabetes mellitus (DM; ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), ischemic heart disease (IHD, ICD-9-CM 410-414), and renal disease (ICD-9-CM 580-589) were identified before the index date to deal with the potential confounding risk factors for GERD. The prescribed medications, namely aspirin, warfarin, clopidogrel, and dipyridamole, were prescribed within 90 days before the date of the end point.

Statistical Analysis

Summary statistics are expressed as frequencies and percentages for categorical variables and as mean and standard deviations for continuous variables. The chi-square and Student *t*-tests were used to analyze categorical and continuous variables, respectively, when comparing the stroke and nonstroke groups. We calculated person-years for each patient until GERD diagnosis, December 31, 2011, or insurance termination. We plotted the cumulative incidence curves of GERD by using the Kaplan-Meier method for the study groups and assessed their differences by using the log-rank test. The incidence density was calculated by dividing the number of newly diagnosed GERD cases by the number of person-years. Univariate and multivariate Cox proportional hazards regression models were used to assess the risk of GERD and GERD-associated risk factors. We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of GERD to evaluate the independent effect of stroke.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). All *P* values were reported from 2-sided tests, in which statistical significance was set at .05.

Results

Between 2000 and 2006, 18,412 and 18,412 patients were included in the stroke and nonstroke groups, respectively. In the stroke group, the mean patient age was 67.8

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