

# The Impacts of Peptic Ulcer on Stroke Recurrence

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**Background:** Peptic ulcer has been associated with an increased risk of stroke. This study aimed to evaluate the impacts of peptic ulcer on stroke recurrence and mortality. **Subjects and Methods:** Patients with first-ever ischemic stroke were retrospectively confirmed with or without a history of peptic ulcer. The primary end point was defined as fatal and nonfatal stroke recurrence. Risks of 1-year fatal and nonfatal stroke recurrence were analyzed with the Kaplan–Meier method. Predictors of fatal and nonfatal stroke recurrence were evaluated with the Cox proportional hazards model. **Results:** Among the 2577 enrolled patients with ischemic stroke, 129 (5.0%) had a history of peptic ulcer. The fatal and nonfatal stroke recurrence within 1 year of the index stroke was higher in patients with peptic ulcer than in patients without peptic ulcer (12.4% versus 7.2%,  $P = .030$ ). Cox proportional hazards model detected that age (hazard ratio [HR] = 1.018, 95% confidence interval [CI] 1.005–1.031,  $P = .008$ ), hypertension (HR = 1.397, 95% CI 1.017–1.918,  $P = .039$ ), and history of peptic ulcer (HR = 1.853, 95% CI 1.111–3.091,  $P = .018$ ) were associated with stroke recurrence. **Conclusions:** Ischemic stroke patients with peptic ulcer may have an increased risk of stroke recurrence. The results emphasize the importance of appropriate prevention and management of peptic ulcer for secondary stroke prevention. **Key Words:** Peptic ulcer—ischemic stroke—recurrence—death.

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## Introduction

Peptic ulcer is a common gastrointestinal disease, with a prevalence of 5%–10% and an incidence of .1%–.3% in general population.<sup>1–3</sup> Ischemic stroke is a common vascular disease with an age-adjusted prevalence of 299 per 100,000 persons and a mortality of 57 per 100,000 persons.<sup>4</sup> The 2 conditions have been associated with each other since 1950.<sup>5</sup> Recent studies established peptic ulcer as a potential risk factor for ischemic stroke.<sup>6–8</sup> A Swedish study reported a 1.21 times increment of risk of ischemic stroke in patients with peptic ulcer.<sup>6</sup> The results were confirmed by a recent study, which indicated that peptic ulcer may increase the subsequent risk of ischemic stroke by 31% in 4 years.<sup>7</sup> Shared risk factors, such as *Helicobacter pylori* infection, disadvantageous socioeconomic status, and

increased psychological stress, have been proposed as the cause of the high concomitant rate of peptic ulcer and stroke.<sup>8</sup>

Based on the results from current studies, we hypothesize that ischemic stroke patients with history of peptic ulcer have a higher risk of recurrence. To test this hypothesis, we evaluated the impact of history of peptic ulcer on stroke recurrence in a large cohort of Chinese patients.

## Subjects and Methods

### *Study Sample*

Patients with first-ever ischemic stroke were prospectively enrolled via Nanjing Stroke Registry Program from January 2014 to May 2016. Stroke was diagnosed according to the criteria of the World Health Organization: rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.<sup>9</sup> Ischemic stroke was classified into 4 subtypes according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.<sup>10</sup>

Patients were enrolled in this study if they (1) had a first-ever ischemic stroke in 7 days; (2) aged 18 years or older; and (3) had the corresponding changes on computed tomography or magnetic resonance image to support the diagnosis of ischemic stroke. Patients were excluded if they (1) had concomitant subarachnoid or intracerebral hemorrhage; (2) had malignant tumor; and (3) had severe heart, lung, and renal diseases. The study protocol was approved by the Ethical Review Board of Jinling Hospital.

### *Baseline Assessment*

Within 24 hours of admission, history of peptic ulcer and elimination treatment of *H pylori* were investigated with a brief questionnaire. Because symptoms of peptic ulcer disease are nonspecific, the result of endoscopy examination is the gold standard for diagnosing peptic ulcer. Meanwhile, detection of *H pylori* is essential for supporting the diagnosis of the peptic ulcer and for initiating the eradication treatment.<sup>3</sup> This study selected only those patients with peptic ulcer diagnosed with endoscopy and those with a history of peptic ulcer received *H pylori* elimination treatment in recent 5 years before the index stroke. Severity of stroke was evaluated with the National Institutes of Health Stroke Scale (NIHSS).

### *End Points and Follow-Up*

The primary end point was defined as fatal and non-fatal stroke recurrence. Recurrent stroke was defined as a cerebrovascular event subsequent to the initial stroke that clearly resulted in a new deficit lasting more than 24 hours and was not attributable to edema, mass effect,

brain shift syndrome, or hemorrhagic transformation of the index cerebral infarction.<sup>11</sup> We defined nonfatal stroke as hospital admission due to stroke that did not lead to death in the same month.<sup>12</sup> Regular follow-up was carried out in 1, 3, 6, 9, and 12 months after the index stroke via telephone interviews or a clinical visit. For telephone interviews, a standardized questionnaire was used. In some cases, family members or caregivers were asked to complete the questionnaire for identifying the time of recurrence or death. In cases with nonfatal recurrence, patients were always encouraged for a clinical visit. Death depended on the help of death certificates, medical records, and family interviews. Where necessary, cause of death was determined by consensus among the study physicians.

### *Statistical Analysis*

Continuous variables were presented as means and standard deviations or median and interquartile ranges. Categorical data were presented as numbers and percentages. Continuous variables were compared using Student's *t* test or one-way analysis of variance. Categorical data or frequencies were compared using  $\chi^2$  test or Fisher's exact test as appropriate. Kaplan-Meier analysis was used to estimate the risk of recurrence between groups. Differences in survival curves were tested with the log-rank test. Cox proportional hazards model was used to evaluate factors that contribute to recurrence or death. A 2-sided *P* value of less than .05 was considered as statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences version 16.0 (SPSS Inc, Chicago, IL).

## Results

A total of 2577 patients with first-ever ischemic stroke were enrolled. Of the 2577 patients enrolled, 655 (25.4%) patients were examined with endoscopy in 5 years before the index stroke, of which 120 (4.7%) were diagnosed with peptic ulcer by endoscopy and 9 (.3%) could not provide endoscopy examination results, but there were records to indicate a clear history of *H pylori* elimination treatment. Therefore, 129 (5.0%) patients were confirmed with a history of peptic ulcer before the index stroke. There were no significant differences concerning age, gender, hypertension, diabetes mellitus, atrial fibrillation, current smoking, and NIHSS score at baseline between patients with and without peptic ulcer. More patients with peptic ulcer lived in rural area than patients without peptic ulcer (38.0% versus 28.4%, *P* = .019). More patients with peptic ulcer had an index stroke of large-artery atherosclerosis etiology (79.1% versus 68.9%, *P* = .014) and fewer with stroke of small-artery occlusion etiology (7.8% versus 18.9%, *P* = .001). Patients with peptic ulcer had higher percentage of neutrophil at baseline than those without peptic ulcer (*P* = .012). Proton pump inhibitor use was more prev-

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