The Impacts of Peptic Ulcer on Functional Outcomes of Ischemic Stroke

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Background and Purpose: Studies have shown that peptic ulcer increased the risk of ischemic stroke and stroke recurrence. This study aimed to evaluate the impacts of peptic ulcer on functional outcomes of ischemic stroke. *Methods:* Patients with first-ever ischemic stroke were grouped as with and without history of peptic ulcer. Functional outcomes were evaluated with modified Rankin scale at 90 days after the index stroke. Favorable functional outcomes were defined as with a modified Rankin scale score of 0-2. Logistic regression was used to identify predictors for favorable functional outcomes at 90 days. *Results:* Among the 2577 enrolled patients with ischemic stroke, 129 (5.0%) had a history of peptic ulcer. The proportion of favorable outcome was higher in patients without peptic ulcer than those with (59.3% versus 42.6%, $P < .001$). Multivariate logistic analysis detected that history of peptic ulcer (odds ratio [OR] = 2.89, 95% confidence interval [CI], 1.03-8.10, $P = .043$), National Institute of Health Stroke Scale score (OR = 2.11, 95% CI, 1.79-2.48, $P < .001$), and large-artery atherosclerosis stroke subtype (OR = 4.08, 95% CI, 1.11-15.03, $P = .035$) decreased the likelihood of favorable outcomes. *Conclusions:* Ischemic stroke patients with peptic ulcer may have an increased risk of less favorable neurological outcome at 90 days after the index stroke.

Key Words: Peptic ulcer—ischemic stroke—mRS score—prognosis

Introduction

Peptic ulcer is a common disease. Lifetime prevalence of peptic ulcer is about 5%-10%, and incidence is about .1%-.3% per year in the general population.[1-3] Stroke is also a common disease. The Global Burden of Diseases study showed that there were 6.9 million new ischemic stroke, 18.2 million ischemic stroke survivors, 3.3 million deaths, and 65.5 million disability adjusted life years due to ischemic stroke in 2013.[4] Accumulating evidence suggested that peptic ulcers may increase the risk of ischemic stroke.[5-7] Our previous study also indicated that peptic ulcer may increase the risk of stroke recurrence.[8]

However, the impacts of peptic ulcer on functional outcomes of ischemic stroke have not been evaluated to date. Based on results from the previous studies, we hypothesis that ischemic stroke patients with history of peptic ulcer may have less favorable neurological outcomes. To test this hypothesis, we evaluated the impact of history of peptic

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ulcer on neurological outcome in a large cohort of Chinese patients.

Subjects and Methods

Study Sample

We prospectively recruited patients with first-ever ischemic stroke via Nanjing Stroke Registry Program from January 2014 to May 2016. Ischemic stroke was diagnosed in patients whose symptoms lasted for at least 24 hours, and whose brain imaging showed either evidence of a relevant ischemic lesion, and excluded intracranial hemorrhage and stroke mimics.[9] Ischemic stroke was classified into 4 subtypes according to Trial of Org 10172 in Acute Stroke Treatment criteria.[10]

Patients were included if they: (1) aged 18 years or older; (2) had first-ever ischemic stroke diagnosed within 7 days of onset; (3) had ischemic changes on computed tomography or magnetic resonance image. Patients were excluded if they: (1) had concomitant subarachnoid or intracerebral hemorrhage; (2) had a prestroke modified Rankin scale (mRS) score more than 2; (3) had malignant tumor; (4) had severe heart, lung, renal, or liver diseases. Written informed consent was obtained from each participant. The study protocol was approved by the Ethical Review Board of Jinling Hospital.

Baseline Assessment

Demographic characteristics, such as presences of major vascular risk factors, concurrent illness, and medication usage, were collected and categorized. Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) at admission. The mRS was used for assessing functional outcomes at 90 days.

Within 24 hours of admission, possible peptic ulcer history and relative treatments were assessed with a brief questionnaire. Considering that symptoms of peptic ulcer are nonspecific and patient-reported peptic ulcer history may be unreliable, this study only selected patients with peptic ulcer being diagnosed with endoscopy or those received *Helicobacter pylori* elimination treatment during the 5 years before the index stroke.

End Points and Follow-Up

All enrolled patients were followed at 90 days of the index stroke. The primary end point was mRS score. A favorable functional outcome was defined as a mRS score of 0-2 at 90 days. The secondary end point was all-cause mortality at 90 days. Death was determined with help of vital certificates, medical records, and family interviews.

Statistical Analysis

Means and standard deviations (SD) were analyzed for parameters conforming to normal distribution. Median and interquartile ranges were analyzed for parameters not conforming to normal distribution. Numbers and percentages were calculated for categorical data. Continuous variables were analyzed with Student's t test or one-way ANOVA. Categorical parameters were tested with χ^2 test or Fisher exact test. Ordinal logistic regression analysis was used to estimate an effect of peptic ulcer across the entire range of mRS scores. Logistic regression models were used to evaluate factors of 90-day outcome, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P value of less than .05 of 2 sides was considered as statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL).

Results

Of the 2577 patients enrolled, 129 (5.0%) were identified with and 2448 (95.0%) without history of peptic ulcer before the index stroke. No significant differences were detected concerning age, gender, hypertension, diabetes mellitus, atrial fibrillation, current smoking, and baseline NIHSS scores between patients with and without peptic ulcer. Patients with peptic ulcer had higher percentage of neutrophil (67.2% versus 64.3%, $P = .012$), higher levels of serum C-reactive protein (15.6 mg/L versus 9.9 mg/L, $P = .001$). Proportion of proton pump inhibitor usage was higher in patient with peptic ulcer than those without (35.7% versus 15.4%, $P < .001$). Proportion of patients with large-artery atherosclerotic stroke was higher in patients with peptic ulcer than those without (79.1% versus 68.9%, $P = .014$). Patients with peptic ulcer had a lower favorable functional outcome (mRS, 0-2, 42.6% versus 59.3%, $P < .001$, Table 1, Fig 1), and higher overall mortality (5.4% versus 1.6%, $P = .001$, Table 1) at 90 days than patients without peptic ulcer (Table 2).

Multivariate logistic analysis showed that history of peptic ulcer (OR = 2.89, 95% CI, 1.03-8.10, $P = .043$), NIHSS score (OR = 2.11, 95% CI, 1.79-2.48, $P < .001$), and large-artery atherosclerosis stroke subtype (OR = 4.08, 95% CI, 1.11-15.03, $P = .035$, Table 3) were associated with favorable neurological outcomes.

Discussion

This study observed that the ratio of favorable neurological outcome at 90 days was lower in ischemic stroke patients with peptic ulcer than those without (42.6% versus 59.3%, $P < .001$). Multivariate logistic analysis detected that peptic ulcer decreased the likelihood of 90-day favorable outcomes (OR = 2.89, 95% CI, 1.03-8.10, $P = .043$).

It has long been noticed that patients with peptic ulcer had an increased risk of atherosclerotic diseases. Some autopsy studies indicated that patients with peptic ulcer had a significant excess of coronary artery disease.[11,12] A recent necropsy survey in military stuffs showed that the dramatic decline of heart attacks in the United States is temporally synchronized with the decline of duodenal ulcer.[13]

Table 1. *Characteristics and outcomes of enrolled patients with and without peptic ulcer*

Characteristics	Peptic ulcer		
	With (n = 129)	Without (n = 2448)	*P* value
Age, years, mean (SD)	60.5 (10.1)	59.9 (11.6)	.594
Male gender, n (%)	90 (69.8)	1753 (71.6)	.651
Rural residence, n (%)	49 (38.0)	695(28.4)	.019
Hypertension, n (%)	87 (67.4)	1553 (63.4)	.357
DM, n (%)	30 (23.3)	588 (24.0)	.843
AF, n (%)	5 (3.9)	85 (3.5)	.808
Current smoking, n (%)	54 (41.9)	946 (38.6)	.465
Baseline measurements			
NIHSS score, median (IQR)	3.0 (1-8)	4.0 (2-9)	.055
Leukocyte,10^9/L, mean (SD)	7.7 (2.6)	7.3 (2.4)	.078
Neutrophil percentage, mean (SD)	67.2 (10.6)	64.3 (10.4)	.012
C-reactive protein, mg/l, mean (SD)	15.6 (12.5)	9.9 (12.3)	.001
Homocysteine, mmol/l, mean (SD)	18.0 (11.4)	16.2 (5.8)	.282
Stroke subtypes			.011
Small-artery occlusion, n (%)	10 (7.8)	462 (18.9)	.001
Large-artery atherosclerosis, n (%)	102 (79.1)	1686 (68.9)	.014
Cardioembolism, n (%)	5 (3.9)	59 (2.4)	.297
Other types, n (%)	12 (9.3)	241 (9.8)	.029
Treatments			
Antithrombotic treatment			.193
antiplatelets, n (%)	125 (96.9)	2409 (98.4)	
Anticoagulants, n (%)	4 (3.1)	39 (1.6)	
Thrombolysis, n (%)	2 (1.6)	98 (4.0)	.160
Proton pump inhibitor use, n (%)	46 (35.7)	378 (15.4)	<.001
Clinical outcomes			
mRS at 90 days			<.001
0-2	55 (42.6)	1452 (59.3)	
3-6	74 (57.4)	996 (40.7)	
Death 3 at 90 days	7 (5.4)	38 (1.6)	.001
Upper gastrointestinal bleeding	5(3.9)	30(1.2)	.011

Abbreviations: AF, atrial fibrillation; DM, diabetic mellitus; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

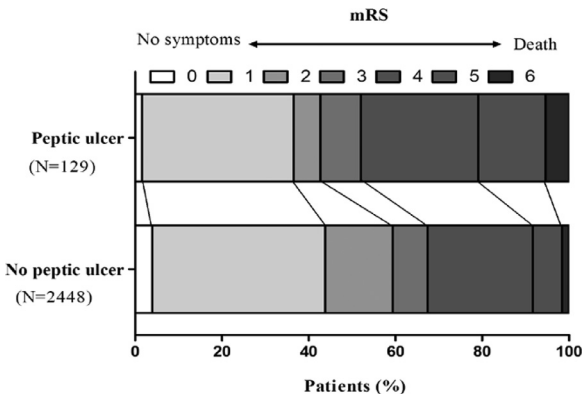

Figure 1. *Distribution of modified Rankin scale (mRS) scores at 90 days in patients with and without peptic ulcer. Favorable neurological outcome was proportionally lower in patients with peptic ulcer than in patients without (42.6% versus 59.3%, P < .001).*

H pylori infection has long been identified as a major risk for peptic ulcer,[14] and *H pylori* infection may induce atherosclerotic diseases. *H pylori* and their DNA have been detected in atherosclerotic plaques.[15,16] Cross-sectional studies suggested a possible relationship between *H pylori* infection and atherosclerotic coronary disease[17,18] or ischemic stroke.[19,20] *H pylori* can infect and survival insidiously in the gastric mucosa, and therefore, generate acute and chronic inflammatory responses.[14,21,22] Inflammatory can initiate and promote atherogenesis.[23] *H pylori* infection can recruit neutrophils, macrophages, dendritic cells, T cells, and B cells and up-regulate C reaction protein (CRP), interleukin (IL)-8, tumor necrosis factor (TNF)-α, IL-6, IL-1β, and interferon (IFN)-γ.[24-27] Some studies suggested that high neutrophil counts are associated with infarct severity and growth and poor neurologic outcome.[28-31] Recent studies suggested that the neutrophil to lymphocyte ratio, as an established marker of systemic inflammation, predicts short- and long-term outcome in stroke patients.[32,33] In this study, both percentage of neutrophil and higher C-reactive protein were higher in patients with peptic ulcer than in patients without. These results can be explained by that the increased

Table 2. *Characteristics of enrolled patients according to clinical outcomes*

Characteristics	mRS		*P* value
	0-2 (n = 1507)	3-6 (n = 1070)	
Age, years, mean (SD)	59.2 (11.5)	61.1 (11.6)	<.001
Male gender, n (%)	1099 (72.9)	744 (69.5)	.060
Rural residence, n (%)	416 (27.6)	328(30.7)	.092
Hypertension, n (%)	972 (64.5)	668(62.4)	.282
History of peptic ulcer	57(3.8)	72 (6.7)	.001
DM, n (%)	368 (24.4)	250 (23.4)	.537
AF, n (%)	26 (1.7)	64 (6.0)	<.001
Current smoking, n (%)	582 (38.6)	418 (39.1)	.819
Baseline measurements			
NIHSS score, median (IQR)	1.0 (0-3)	8.5.(5.8-12.0)	<.001
Leukocyte,10^9/L, mean (SD)	6.8 (1.9)	8.0 (2.9)	<.001
Neutrophil percentage, mean (SD)	62.0 (9.1)	68.8 (10.8)	<.001
Low-density lipoprotein, mean (SD)	2.4 (1.0)	2.6 (.9)	<.001
Triglycerides, mean (SD)	1.53 (.9)	1.65 (1.3)	.009
C-reactive protein, mg/l, mean (SD)	9.2 (12.3)	12.8 (12.5)	.004
Homocysteine, mmol/l, mean (SD)	17.6 (10.5)	18.5 (12.1)	.220
Stroke subtypes			<.001
Small-artery occlusion, n (%)	329 (21.8)	143 (13.4)	
Large-artery atherosclerosis, n (%)	1004 (66.6)	784 (73.3)	
Cardioembolism, n (%)	13 (.9)	51 (4.8)	
Other types, n (%)	161 (10.7)	92 (8.6)	
Treatments			
Antithrombotic treatment			.014
Antiplatelets, n (%)	1493 (57.9)	1041 (31.6)	
Anticoagulants, n (%)	14 (.9)	29 (2.7)	
Thrombolysis, n (%)	37 (2.5)	58 (5.4)	<.001
Statin therapy, n (%)	1471 (97.6)	1040 (97.2)	.511
Proton pump inhibitor use, n (%)	259 (17.2)	165 (15.4)	.233

Abbreviations: AF, atrial fibrillation; DM, diabetic mellitus; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

inflammation in patients with peptic ulcer may contribute to poor prognosis of ischemic stroke.

Etiologic subtypes of ischemic stroke may affect early prognosis of ischemic stroke. Patients with large-artery atherosclerosis stroke had poorer functional outcomes than patients with stroke cause by small artery disease.[34,35] In this study, 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%, $P = .001$). Large-artery atherosclerosis stroke subtype (OR = 4.08, 95% CI, 1.11-15.03, $P = .035$) was associated with increased risk of less favorable neurological outcome. This result can partially explain that the impacts of peptic ulcer on stroke prognosis.

Differences in antiplatelet therapy strategies may partially explain differences in neurological outcomes at 90 days. Patients with previous history of peptic ulcer or

Table 3. *Multivariate analysis of poor function for ischemic stroke*

Risk and variables	Increment/categories	OR (95% CI)	*P* value
History of peptic ulcer	Versus without	2.89 (1.03-8.10)	.043
NIHSS score	One score increment	2.11 (1.79-2.48)	<.001
Stroke subtypes			.0356
Large-artery atherosclerosis	Versus small-artery occlusion	4.08 (1.11-15.03)	.035
Cardioembolism	Versus small-artery occlusion		.874
Other types	Versus small-artery occlusion		.226

Abbreviations: CI, interval confidence; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio.

Logistic regression analyses were adjusted for age, atrial fibrillation, leukocyte, neutrophil percentage, low-density lipoprotein, triglycerides, C-reactive protein, antithrombotic treatment, and thrombolysis.

upper gastrointestinal bleeding have a higher risk of upper gastrointestinal bleeding when taking low-dose aspirin.[36,37] Low-dose aspirin is an independent risk factor for upper gastrointestinal bleeding in patients with gastric and duodenal ulcers (OR = 1.80, 95% CI, 1.18-2.75), and the combination of low-dose aspirin and other nonaspirin antiplatelet drugs increases the risk of upper gastrointestinal bleeding (OR = 6.70, 95% CI, 1.83-24.50).[38] Our study also showed that ischemic stroke patients with a history of peptic ulcer had higher upper gastrointestinal bleeding (3.9% versus 1.2%, $P = .011$). Therefore, antiplatelet therapy for ischemic stroke patients with a history of peptic ulcer will increase the risk of upper gastrointestinal bleeding, and this risk will further increase when combined with antiplatelet therapy. For ischemic stroke patients with a history of peptic ulcer, cautious antiplatelet therapy is often adopted due to the fear of gastrointestinal bleeding. The cautious antiplatelet therapy is likely to increase the risk of less favorable neurological outcome for patients with ischemic stroke.

Differences in use proton pump inhibitor may also partly explain the varied risk of stroke prognosis. Proton pump inhibitors are often prescribed in combination with antiplatelet therapy to prevent gastrointestinal bleeding, especially in patients with a history of peptic ulcer.[39] In this study, patients with peptic ulcer were more likely to use proton pump inhibitor than patients without (35.7% versus 15.4%, $P < .001$). However, some evidences suggested that as competitive inhibitors of cytochrome P450 pathway, proton pump inhibitors can attenuate the antiplatelet effect of clopidogrel.[40,41] Therefore, proton pump inhibitors may affect the prognosis of ischemic stroke by weakening the role of antiplatelet drugs.

Disadvantageous socioeconomic status may be a shared risk of peptic ulcer and ischemic stroke, and contribute substantially to their coexistence. Johnsen et al reported that individuals with low educational levels had increased risk of peptic ulcer.[42] On the other hand, several studies observed an association between atherosclerotic diseases and socioeconomic status. A study reported association between socioeconomic status and carotid intima-media thickness.[43] Disadvantageous adulthood socioeconomic status was also associated with increased risk of stroke.[44] Our study observed that stroke patients with peptic ulcer were more likely to live in rural areas than those without peptic ulcer ($P = .019$).

Several limitations of the present study must be addressed when interpreting the results. First, a history of peptic ulcer was retrospectively confirmed, which may generate memory biases especially in elderly patients. And there was a lack of information about the type, size, and severity of the peptic ulcer. Second, we only considered the previous history of peptic ulcer, but did not determine whether there was active peptic ulcer at the time of admission, let alone the peptic ulcer caused by first-ever ischemic stroke. Third, some patients may have peptic ulcer undiagnosed due to the mildness of symptoms or disadvantageous conditions. This may lead to bias in this study. Finally, this study is a single-center study, and the results may not be extended to other populations.

Conclusion

Ischemic stroke patients with peptic ulcer may have an increased risk of less favorable neurological outcome at 90 days after the index stroke.

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