

Factors affecting the occurrence of gastrointestinal bleeding in acute ischemic stroke patients

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Abstract

Gastrointestinal bleeding (GIB) is a common complication that occurs after stroke, and GIB may negatively affect patient prognosis. In this study, we aimed to examine:

- (1) the risk factors of GIB in acute cerebral infarction patients;
- (2) association between GIB and 1-year mortality in patients with acute cerebral infarction.

Patients with acute cerebral infarction were divided into 2 groups based on the occurrence of GIB during acute stroke stage. Patient characteristics, clinical presentation, stroke risk factors, comorbidities, laboratory data, medication, and outcomes were investigated to analyze the associations between the variables and the probability of having GIB. In addition, patients in the study were matched individually by age, gender. A 1:1 matched case-control method and conditional logistic regression models for single and multiple factors were used to assess the risk factors of GIB in acute cerebral infarction patients.

Clinical data of patients with acute cerebral infarction were reviewed and analyzed during the years 2015 and 2016. Finally, 1662 patients with acute cerebral infarction were included in this study, of whom 139 (8.5%) patients had GIB at admission. Multivariate logistic regression analysis revealed that the independent risk factors for GIB in patients with acute cerebral infarction were advanced age (OR=1.030, $P=.009$), low Glasgow Coma Scale (GSC) score (OR=0.850, $P=.014$), infection (OR=4.693, $P<.001$), high NIHSS score (OR=1.114, $P=.001$), and posterior circulation infarction (OR=4.981, $P=.010$). The case-control study ultimately included 136 case-control pairs. Stepwise conditional regression analyses revealed that the independent risk factors for GIB in patients with acute cerebral infarction were low Glasgow Coma Scale (GSC) score (RR=0.645, $P=.011$), infection (RR=15.326, $P=.001$), and posterior circulation infarction (RR=6.129, $P=.045$). The group with GIB had a higher rate of mortality and disability level (mRS grade ≥ 4) than the group without GIB ($P<.001$) within 1 year after stroke. In addition, independent risk factors of death within 1 year after stroke in patients were GIB (OR=6.096, $P<.001$), infection (OR=4.493, $P<.001$), mRS grade ≥ 4 (OR=4.129, $P<.001$), and coronary heart disease (OR=3.718, $P=.001$).

GIB is a common complication after ischemic stroke. These identified factors may help clinicians identify risks of GIB before it develops. GIB is associated with increased risk of 1-year mortality and poor functional outcome in acute cerebral infarction patients.

Abbreviations: GCS = Glasgow Coma Scale, GIB = gastrointestinal bleeding, IQR = interquartile range, LACI = lacunar Infarct, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, OCSF = Oxfordshire Community Stroke Project, OR = odds ratio, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct, RR = risk ratio, rt-PA = recombinant tissue type Plasminogen Activator, TACI = total anterior circulation infarct.

Keywords: gastrointestinal bleeding, mortality, stroke

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1. Introduction

Gastrointestinal bleeding (GIB) is a common complication that occurs after stroke, and it can negatively influence patient prognosis. Previous literature reports that the incidence of GIB after acute ischemic stroke ranges from 1.24% to 8.6%.^[1–4] In previous studies, clinical factors, such as infection,^[1] being male,^[5] old age,^[1,2,5,6] history of hypertension,^[5,7,8] digestive tract disease history,^[2,5,9,10] and renal function,^[2] were identified as being associated with the risk of GIB after acute stroke. A large sample (3,998,667 cases) study of acute ischemic stroke in the United States showed that being of Asian descent, co-morbidity of peptic ulcer, coagulation dysfunction, water electrolyte disorder, tumor, liver disease, chronic pulmonary disease, hyperthyroidism, arrhythmia, iron deficiency anemia, alcoholism, weight loss, obesity, and depression were all related to the occurrence of GIB.^[4] Although several risk factors for GIB have been identified, few studies have focused on investigating the

influence of GIB during the acute stroke stage on the long-term mortality. Also, we analyzed carotid artery stenosis and intracranial artery stenosis as risk factors for post-stroke GIB, which have not previously been described. This study aimed to examine: (1) the risk factors of GIB in acute cerebral infarction patients; (2) the influence of GIB during the acute stroke stage on the long-term mortality.

2. Materials and methods

2.1. Patients and assessment procedures

We retrospectively reviewed patients who were admitted to the Stroke Unit of the Department of Neurology at Chifeng Municipal Hospital in Inner Mongolia, China with a diagnosis of acute cerebral infarction from January 1, 2015 to December 31, 2016. All of the patients met the following inclusion criteria:

- a) the diagnosis of acute cerebral infarction was made according to the World Health Organization criteria and confirmed by brain computed tomography or magnetic resonance imaging scan;
- b) GIB was defined according to Davenport et al.^[11]

In this study, patients were divided into 2 groups according to the presence or absence of GIB during acute stroke stage. The clinical details and follow up results for 1-year were retrospectively analyzed. Major medical problems (e.g., death, stroke, functional or disability level of the patients after stroke, infection, cardiovascular diseases, etc.) were evaluated. Patients were excluded if the case and follow-up notes were incomplete. The ethics committee of Chifeng municipal hospital approved the study protocol.

The following clinical details were analyzed:

1. gender and age;
2. current smoking (>1 year, >5 cigarettes per day), excessive alcohol consumption (>1 year, liquor over 40 degrees >100 ml);
3. medical history: hypertension, diabetes mellitus, atrial fibrillation, coronary heart disease;
4. infection was identified according to clinical symptoms, such as fever, chills, cough, expectoration, urinary frequency, urgent urination, odynuria, and skin suppurate. The diagnosis of infection that was confirmed by laboratory tests and imaging examination;
5. laboratory data within 24 hours: Red blood cell count, white blood cell count, platelet, fasting blood glucose, creatinine, urea nitrogen, uric acid, homocysteine;
6. anti-platelet medication use (aspirin, clopidogrel) or anticoagulant (warfarin) use, prophylactic application of proton pump inhibitors;
7. thrombolysis therapy: intravenous recombinant tissue type plasminogen activator (rt-PA) within 3 hours after onset;
8. stroke subtype according to the Oxfordshire Community Stroke Project (OCSP) criteria^[12] where acute ischemic stroke is classified into lacunar infarct (LACI), total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), and posterior circulation infarct (POCI);
9. stroke severity based on the National Institutes of Health Stroke Scale score (NIHSS) score, conscious state based on the Glasgow Coma Scale (GCS) score;
10. disability level of the patients after ischemic stroke was assessed by the modified Rankin Scale (mRS);

11. carotid artery stenosis and intracranial artery stenosis was identified according to the degree of artery stenosis $\geq 50\%$, which was confirmed by Computed Tomography Angiography.

2.2. Statistical analysis

SPSS 25.0 for Windows was used for data analysis. Continuous variables were expressed as mean \pm standard deviation if the values were normally distributed and analyzed by independent *t* test. Continuous variables were expressed as a median and interquartile range (IQR) if the values were not normally distributed and analyzed by Mann–Whitney tests. Categorical variables were expressed as a number and percentage and compared by the Chi-square test. A *P* value $< .05$ was considered statistically significant. The independent associations between the variables and the probability of death and having GIB were analyzed using unconditional logistic regression. Paired data were analyzed by conditional logistic regression to analyze the associations between the variables and the probability of having GIB.

3. Results

3.1. Patient characteristics

Clinical data of patients with acute cerebral infarction were reviewed and analyzed during the years 2015 and 2016. Finally, 1662 patients with acute cerebral infarction were included in this study. The median age was 70 (range, 55–70) years. Males accounted for 66.6% of the patients. Moreover, 139 (8.4%) patients had GIB after admission. In the case-control study, case and control subjects were matched at 1:1 by age (± 2 years) and sex. The case-control study ultimately included 136 diagnosed GIB patients and 136 control subjects: 99 pairs were males and 37 pairs were females, aged from 36 to 90 years, with an average age of 67.19 ± 11.33 years old.

3.2. Baseline characteristics and GIB

Advanced age, the prevalence of atrial fibrillation, infection, and carotid artery stenosis was significantly higher among patients with GIB compared to patients without GIB. On clinical presentation of stroke, POCI occurred more frequently in the group with GIB, and the NIHSS score on admission was significantly higher in patients with GIB, whereas the GCS score was significantly lower in patients with GIB. Additionally, fasting plasma glucose and white blood cell count were significantly higher in the group with GIB. On clinical outcomes of stroke, patients experiencing GIB had longer acute hospitalization (21 days vs 15 days, $P < .001$) and higher mortality rates (19.4% vs 1.3%, $P < .001$) than patients without GIB (Table 1).

3.3. Multivariate logistic regression analysis for potential risk of GIB

Multivariate logistic regression analysis showed the independent risk for GIB in patients with acute cerebral infarction were: advanced age, conscious disturbance (low GSC score), severe neurological deficit (high NIHSS score), infection, and posterior circulation infarct (Table 2).

Table 1**Characteristics of patients with or without GIB.**

	Patients with GIB (n=139)	Patients without GIB (n=1523)	P value
Gender male/female	101/38	1006/517	.133
Age ($\bar{x} \pm S$)	67.8 \pm 11.7	61.8 \pm 10.4	<.001
Smoking (n%)	34 (24.5)	415 (27.2)	.549
Excessive alcohol consumption (n%)	18 (12.9)	241 (15.8)	.463
Hypertension (n%)	114 (82.0)	1172 (77.0)	.204
Diabetes mellitus (n%)	29 (20.9)	313 (20.6)	.913
Atrial fibrillation (n%)	15 (10.8)	81 (5.3)	.013
History of stroke (n%)	68 (48.9)	638 (41.9)	.127
Coronary artery disease (n%)	15 (10.8)	152 (10.0)	.768
History of digestive tract disease (n%)	12 (8.6)	77 (5.1)	.077
Infection (n%)	96 (69.1)	165 (10.8)	<.001
Red blood cell ($\bar{x} \pm S$)	4.5 \pm 0.7	4.6 \pm 0.6	.285
White blood cell median (IQR)	10.7 (8.6–13.2)	7.02 (5.7–8.5)	<.001
Platelet median (IQR)	218.0 (171.0–257.7)	209.0 (174.0–247.0)	.683
Fasting blood glucose median (IQR)	6.1 (5.2–8.1)	5.3 (4.7–6.8)	<.001
Uric acid median (IQR)	275.0 (203.0–362.0)	287.0 (230.0–344.0)	.296
Creatinine median (IQR)	74.0 (47.0–87.0)	69.0 (58.0–81.0)	.100
Urea nitrogen median (IQR)	5.7 (4.2–7.6)	5.1 (4.2–6.3)	.053
Homocysteine median (IQR)	14.3 (10.3–20.3)	13.5 (10.4–20.1)	.794
Anti-platelet medication use (n%)	132 (95.0)	1452 (95.3)	.833
Anticoagulant use (n%)	5 (3.6)	61 (4.0)	1.000
Proton pump inhibitors use (n%)	27 (19.4)	203 (13.3)	.054
Thrombolysis therapy (n%)	11 (7.9)	68 (4.5)	.091
Carotid artery stenosis (n%)	45 (32.4)	281 (18.5)	<.001
Intracranial artery stenosis (n%)	39 (28.1)	443 (29.1)	.846
Mortality (n%)	27 (19.4)	20 (1.3%)	<.001
Length of hospitalization (days) median (IQR)	21 (11–34)	15 (12–19)	<.001
GCS median (IQR)	15 (15–15)	11 (7–15)	<.001
NIHSS median (IQR)	14 (5–20)	3 (2–6)	<.001
OCSP subtype (n%)			<.001
TACI	30 (21.6)	106 (7)	
PACI	39 (28.1)	875 (57.5)	
POCI	67 (48.2)	278 (18.3)	
LACI	3 (2.2)	264 (17.3)	

GCS = Glasgow Coma Scale, GIB = gastrointestinal bleeding, IQR = inter quartile range, LACI = lacunar infarct, NIHSS = National Institutes of Health Stroke Scale Score, OCSP = Oxfordshire Community Stroke Project, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct, TACI = total anterior circulation infarct.

3.4. Univariate conditional logistic regression analysis for potential risk of GIB

Univariate conditional logistic regression showed that Infection, fasting blood glucose, history of digestive tract

disease, low GSC score, high NIHSS score, total anterior circulation infarct, and posterior circulation infarct had correlation with GIB in acute cerebral infarction patients (Table 3).

Table 2**Multivariate logistic regression analysis for potential risk factors of GIB.**

Dependent variable	Covariate	β -coefficient	Odds ratio	95%CI	P value
GIB	Age	0.030	1.030	1.007–1.054	.009
	Atrial fibrillation	0.488	1.628	0.770–3.442	.202
	Infection	1.546	4.693	2.837–7.765	<.001
	Fasting blood glucose	0.059	1.061	0.978–1.151	.153
	GCS	−0.162	0.850	0.747–0.968	.014
	NIHSS	0.108	1.114	1.047–1.185	.001
	Carotid artery stenosis	0.354	1.424	0.863–2.350	.166
	OCSP subtype				
	LACI				
	TACI	−0.092	0.912	0.230–3.619	.896
	PACI	0.356	1.428	0.417–4.893	.570
POCI	1.606	4.981	1.462–16.969	.010	

GCS = Glasgow Coma Scale, GIB = gastrointestinal bleeding, LACI = lacunar infarct, TACI = total anterior circulation infarct, NIHSS = National Institutes of Health Stroke Scale Score, OCSP = Oxfordshire Community Stroke Project, PACI = partial anterior circulation infarct, POCI = posterior circulation infarct.

Table 3**Univariate conditional logistic regression analysis for potential risk factors of GIB.**

Variables	β -coefficient	Risk ratio	95%CI	P value
Smoking	0.560	1.750	0.947–3.234	.074
Excessive alcohol consumption	0.305	1.357	0.680–2.707	.386
Hypertension	0.405	1.500	0.826–2.723	.183
Diabetes mellitus	0.043	1.043	0.589–1.849	.884
Atrial fibrillation	−0.606	0.545	0.270–1.102	.091
Coronary artery disease	0.080	1.083	0.494–2.374	.842
History of digestive tract disease	1.204	3.333	1.583–7.021	.002
Infection	3.795	44.500	10.958–180.707	<.001
Red Blood Cell	0.139	1.149	0.771–1.71	.495
Platelet	−0.003	0.997	0.993–1.001	.119
Fasting blood glucose	0.393	1.481	1.252–1.752	<.001
Uric acid	−0.001	0.999	0.996–1.001	.271
Creatinine	0.001	1.001	0.991–1.010	.896
Urea nitrogen	0.062	1.064	0.951–1.190	.281
Homocysteine	−0.011	0.989	0.969–1.011	.334
Anti-platelet medication use	1.344	3.833	1.561–9.414	.003
Proton pump inhibitors use	0.047	1.048	0.576–1.905	.879
Intracranial artery stenosis	0.065	1.067	0.648–1.755	.800
Carotid artery stenosis	0.560	1.750	1.010–3.031	.046
GCS	−0.699	0.497	0.362–0.684	<.001
NIHSS	0.228	1.257	1.161–1.360	<.001
OCSP subtype				
LACI				
TACI	4.265	71.199	10.697–473.881	<.001
PACI	1.243	3.464	0.977–12.287	.054
POCI	2.581	13.210	3.553–49.110	<.001

GCS=Glasgow Coma Scale, GIB=gastrointestinal bleeding, LACI=lacunar infarct, NIHSS=National Institutes of Health Stroke Scale Score, OCSP=Oxfordshire Community Stroke Project, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct, TACI=total anterior circulation infarct.

3.5. Multivariate conditional logistic regression analysis for potential risk of GIB

After adjusting for the potential risk factors ($P < .1$) in the univariate conditional logistic regression) in a backward, stepwise multivariate conditional logistic regression, only low Glasgow Coma Scale (GCS) score, infection, and posterior circulation infarction were positively associated with patients having GIB during acute ischemic stroke (Table 4).

3.6. Mortality and disability rate within 1-year after stroke

At the end of the 1-year observation period, 47 patients had died (2.8%), including 27 (24.1%) in the group with GIB and 20 (1.3%) in the group without GIB. 101 patients had mRS grade ≥ 4 within 1-year after acute stroke, including 50 (35.9%) in the group with GIB and 51 (3.3%) in the group without GIB. The

Chi-square test revealed that the group with GIB had a higher rate of mortality than the group without GIB ($P < .001$) within 1-year after stroke. Also, the group with GIB had a higher disability level (mRS grade ≥ 4) than the group without GIB ($P < .001$).

3.7. Multivariate logistic regression analysis for potential risk of mortality within 1-year after stroke

GIB, high disability the patients (mRS grade ≥ 4), infection, and coronary heart disease were independent risk of mortality within 1-year after acute cerebral infarction (Table 5).

4. Discussion

Gastrointestinal bleeding is an important cause of increased mortality in patients with acute cerebrovascular disease.^[1,2,9,13,14] The incidence of GIB after acute ischemic stroke

Table 4**Multivariate conditional logistic regression analysis for potential risk factors of GIB.**

Variables	β -coefficient	Risk ratio	95%CI	P value
Infection	2.730	15.326	3.254–72.185	.001
GCS	−0.439	0.645	0.460–0.904	.011
OCSP subtype				
LACI				.036
TACI	1.504	4.498	0.294–68.893	.280
PACI	0.160	1.174	0.262–5.261	.083
POCI	1.813	6.129	1.045–35.963	.045

GCS=Glasgow Coma Scale, GIB=gastrointestinal bleeding, LACI=lacunar infarct, OCSP=Oxfordshire Community Stroke Project, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct, TACI=total anterior circulation infarct.

Table 5**Multivariate logistic regression analysis for potential risk factors of mortality within 1 year after stroke.**

Dependent variable	Covariate	β -coefficient	Odds ratio	95%CI	P value
Mortality	GIB	1.808	6.096	3.007–12.361	<.001
	Infection	1.502	4.493	2.048–9.856	<.001
	mRS grade \geq 4	1.418	4.129	2.089–8.163	<.001
	Coronary artery disease	1.313	3.718	1.672–8.269	.001
	Age	0.013	1.013	0.982–1.046	.416

GIB = gastrointestinal bleeding, mRS = modified Rankin Scale.

is 8.4% in our study. GIB occurred at a mean of 5.7 days after stroke in our study. Our study found that old age,^[1,2,5,6] a high NIHSS score,^[2,5,7–9] a low GCS score,^[5,6,11,15] infection,^[1] and posterior circulation infarction^[5] may be the independent risk factors for GIB in patients with acute cerebral infarction. Infection, low GCS score, and posterior circulation infarction were confirmed by the subsequent 1:1 matched case-control study. These factors have been confirmed by previous studies.

The mechanism of acute cerebral infarction combined with GIB has not been elucidated. Antiplatelet use, stress, vagal hyperactivity and activation of noradrenaline neurons were proposed as pathophysiological mechanisms involved in mucosal injury after ischemic stroke. Besides, interruption of the axis between the central nervous system and the digestive system due to stroke may increase the risk of mucosal injury in the digestive system. Therefore, severe ischemic stroke and posterior circulation ischemia are possibly associated with an increased risk of GIB. Our study found that the prevalence of carotid artery stenosis was higher in patients with GIB, which have not previously been described. The incidence of GIB after acute ischemic stroke is 13.8% (45/326) in patients with carotid artery stenosis and 7.0% (94/1336) in patients without carotid artery stenosis. There was significant difference between the group with and without carotid artery stenosis ($P < .001$). It may be because that carotid artery stenosis is the main cause of severe ischemic stroke, such as internal carotid artery occlusion, basilar artery occlusion, large cerebral or cerebellar infarction. Conscious disturbance and high NIHSS score typically indicate a severe stroke, while a severe ischemic stroke increases the risk of GIB.^[2] Previous studies showed that the appearance of pneumonia was significantly higher in stroke patients with GIB,^[1] and there was a bidirectional association between GIB and infection.^[4,16] Several in-hospital complications, such as pulmonary embolism, deep venous thrombosis, the urinary tract infection, septicemia, and acute kidney injury, were also thought to have a bidirectional association with GIB.^[4] Early recognition and aggressive management of these complications might be to prevent the event of GIB.

In previous studies, mucosal lesions of GIB after stroke often bleed from superficial mucosal capillaries and usually do not perforate.^[17] Although gastrointestinal bleeding is relatively mild in most patients after stroke, they have to stop antiplatelet drugs. Fasting and gastrointestinal decompression may lead to hemodynamic insufficiency in GIB patients. Bleeding stop antithrombotic treatment, this may lead to a prothrombotic state.^[18] These factors may result in the deterioration of neurological symptoms and poor clinical outcome.

In previous studies, steroid hormones, calcium channel blockers, and nonsteroidal anti-inflammatory drugs have been shown to increase the risk of GIB,^[19–22] and the incidence of GIB

can be reduced by ulcerative prophylaxis and HMG-CoA reductase inhibitors.^[23,24] In this study, the use of antiplatelet medication (aspirin and clopidogrel), anticoagulants (warfarin), and rt-PA were not associated with the risk of GIB and no significant correlation was found between prophylactic application of proton pump inhibitors and GIB. Since the data analyzed in the present study were only limited to the inpatient stay and did not include preadmission records, the impact of the history of the prophylactic application cannot be excluded in the results. Use of routine acid-suppressing drugs as prophylaxis in stroke patients is controversial. However, there is a lack of large randomized controlled studies for ulcer prophylaxis after stroke.

This study showed the association between GIB in the acute stroke stage and increased 1-year mortality in patients with ischemic stroke. Some studies have shown that GIB is associated with increased in-hospital and long-term mortality.^[25,26] This study confirmed the conclusion in patients with ischemic stroke. Also, GIB was associated with a higher disability level within 1-year after stroke. There are less data in the available literature on these issues. The exact mechanisms by which episodes of GIB increase the risk of disability and mortality remain unknown. GIB might reduce and delay the intensity and time of rehabilitation. Therefore, GIB play down the rehabilitation efficacy. GIB might prolong the rehabilitative ward stay.^[6] Prolonged bedridden time increases the incidence of venous thrombosis in the lower extremities, pulmonary embolism, infection, and other complications. These combined reasons resulted in poor long-term prognosis of patients.

This study has limitations. First, our study was the retrospective research design. Thus diagnosis timing and treatments are performed after stroke onset was not controlled but determined by each attending doctor, which may influence the outcome. Second, the source of GIB was not determined because the endoscopic examination could not be done. Third, we did not evaluate the impact of medications, such as glucocorticoids, selective serotonin reuptake inhibitors, and antibiotics, which may influence the outcome.

5. Conclusions

GIB is a common complication that occurs after ischemic stroke. GIB is associated with increased risk of 1-year mortality and poor functional outcome in acute cerebral infarction patients. Independent risk factors for GIB in patients with acute cerebral infarction were advanced age, conscious disturbance, severe neurological deficit, infection, and posterior circulation infarction. These identified factors may help clinicians identify risks of GIB before it develops. Moreover, high disability level, infection, GIB, and coronary heart disease are high-risk factors of mortality within 1-year after acute cerebral infarction.

Author contributions

Conceptualization: Jia Fu.

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Formal analysis: Jia Fu.

Investigation: Jia Fu.

Methodology: Jia Fu.

Project administration: Jia Fu.

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