



# Effect of upper gastrointestinal bleeding on prognosis of middle-aged patients with acute ischemic stroke: a retrospective study

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**Background:** Upper gastrointestinal bleeding (UGIB) is a common complication of acute ischemic stroke (AIS), but the effect of UGIB on the prognosis of middle-aged AIS patients is not clear.

**Methods:** Patients with AIS admitted to our hospital from January 2011 to December 2015 were eligible to be included in this study. All included patients were divided into UGIB and non-UGIB groups. Some clinical characteristics were retrospectively collected. Primary outcomes were all-cause mortality within 1, 3, and 5 years, as well as the incidence of stroke recurrence. Cox proportional hazards regression analyses were used to determine the effect of UGIB on 5-year mortality and the incidence of stroke recurrence. Logistic regression was also used to identify the predictors of UGIB in AIS patients.

**Results:** A total of 405 AIS patients were included in this study and then divided into UGIB and non-UGIB groups. The mean age of the UGIB group and non-UGIB group was 61.5±9.6 and 53.1±14.0 years, respectively ( $P<0.001$ ). The baseline score of the National Institute of Health Stroke Scale (NIHSS) was significantly higher in the UGIB group than in the non-UGIB group ( $P<0.001$ ). AIS patients in the UGIB group had a higher 1-, 3-, and 5-year mortality and a higher incidence of stroke recurrence (all  $P<0.001$ ). Kaplan-Meier curves showed that AIS patients with UGIB had a higher 5-year mortality and a higher incidence of stroke recurrence (both  $P<0.001$ ). Cox proportional hazards regression models indicated that the occurrence of UGIB, older age, a high NIHSS score, and stroke recurrence were related to a higher 5-year mortality. Similarly, the occurrence of UGIB, older age, a high NIHSS score, and hypertension increased the incidence of stroke recurrence. According to the multivariate logistic regression analysis, older age, a high NIHSS score, and previous anticoagulant use were identified as predictors of UGIB.

**Conclusions:** UGIB has important effects on the prognosis of AIS patients. The incidence of UGIB increases with older age, a high NIHSS score, and previous anticoagulant use, which provides important evidence for the treatment and nursing of AIS patients.

**Keywords:** Upper gastrointestinal bleeding (UGIB); acute ischemic stroke (AIS); middle-age; mortality; recurrence

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## Introduction

Acute ischemic stroke (AIS) is a common cerebrovascular disease throughout the world and accounts for two-thirds of all stroke patients (1). More recently, stroke patients are tending to be younger and often have a poor prognosis (2). Over the course of treatment, patients can also develop other complications that adversely affect their prognosis. Upper gastrointestinal bleeding (UGIB) is a common complication of AIS, with an incidence rate of 1.2–8.1% (3–6). Many risk factors are related to the incidence of UGIB, including age, gender, hypertension, history of peptic ulcer, previous UGIB, and stroke subtype (7–9). According to previous studies, UGIB is related to a worse prognosis in AIS patients (10,11). In their retrospective study, Chou *et al.* reported that the occurrence of UGIB increased the 3-year mortality rate of acute stroke patients (10). Du *et al.* also found that UGIB increased the incidence of stroke recurrence after AIS (11).

Most previous studies on the effects of UGIB have focused on the prognosis of elderly patients with AIS. Age has been verified as an important independent risk factor for UGIB, and elderly patients with AIS are more likely to suffer from UGIB than younger patients (7,8). However, the proportion of middle-aged stroke patients has increased in recent years. Although the prognosis for middle-aged stroke patients is better than that of elderly patients (12), the increasing number of middle-aged patients with stroke makes the study of their prognosis an important focus of research. Considering the association between UGIB and prognosis in elderly patients with AIS, it is important to determine whether this relationship is similar in middle-aged stroke patients, but to date this has not been investigated.

This was a retrospective study enrolling AIS patients from a single center to determine mortality and stroke recurrence in middle-aged patients. In addition, the incidence of UGIB was recorded and the effect of UGIB on the prognosis of AIS was determined using a multivariate Cox regression analysis. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-907>).

## Methods

### Study participants

Patients with AIS who were admitted to our hospital from January 2011 to December 2015 and who met the inclusion

and exclusion criteria were included in this study. The diagnosis of AIS was defined according to specific symptoms such as limb weakness, unconsciousness, and syncope, and then confirmed by brain imaging using computed tomography or magnetic resonance. Only middle-aged AIS patients who were 40–65 years old were included in this study. The following patients were excluded: (I) patients with a previous history of AIS; (II) patients who were sent to our hospital after more than 3 days; (III) patients who were transferred to other hospitals or returned home without proper treatment during hospitalization. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Affiliated Hospital of Jiangnan University (No.: 02019050). Written informed consent from patients was not required due to the retrospective nature of the study.

### Study data

All included patients were divided into UGIB and non-UGIB groups. UGIB was defined according to specific symptoms such as hematemesis and melena, and then confirmed by endoscopy. The following data were collected by the investigators: age; gender; baseline score of the National Institute of Health Stroke Scale (NIHSS); stroke subtype [including partial anterior circulation infarct (PACI), total anterior circulation infarct (TACI), lacunar infarction (LACI), and posterior circulation infarct (POCI), confirmed by computed tomography or magnetic resonance]; comorbidities (including hypertension, diabetes mellitus, hyperlipidemia, anemia, coronary artery disease, and liver cirrhosis); history of smoking; history of alcoholism; previous anticoagulant use; previous antiplatelet use; and previous non-steroidal anti-inflammatory drug (NSAID) use. These data were collected by several investigators and summarized by one investigator for screening and sorting.

### Study outcomes

All patients were followed up for a maximum of 5 years. The primary outcomes in this study were all-cause mortality within 1, 3, and 5 years, as well as the incidence of stroke recurrence. Stroke recurrence was defined as any AIS event occurring during the follow-up period. The secondary outcomes included length of hospital stay and in-hospital mortality.

### Statistical analysis

Continuous variables such as age, baseline NIHSS score, and length of hospital stay were reported and expressed as means and standard deviations. Categorical variables such as gender, subtype of stroke, comorbidities, history of smoking and alcoholism, previous drug use, mortality and stroke recurrence were reported and expressed as numbers and percentages. Kaplan-Meier curves and the log-rank test were performed to compare the 1-, 3-, and 5-year mortality rates of the UGIB and non-UGIB groups. Univariate and multivariate Cox proportional hazards models were used to determine the effect of UGIB on 5-year mortality and the incidence of stroke recurrence. In addition, logistic regression was used to identify the predictors of UGIB in AIS patients. All statistical analyses were performed using SPSS 18.0 (IBM Inc. NY, USA) and a P value <0.05 was considered statistically significant.

### Results

According to the inclusion and exclusion criteria, a total of 405 AIS patients were included in this study. Their clinical characteristics are listed in *Table 1*. Because this study only included middle-aged AIS patients, the mean age of included patients was 54.1±13.8 years old. Male patients accounted for 58.5% of the total sample, and the mean NIHSS baseline score for all patients was 4.8±2.7 points. PACI was the most common subtype of AIS. In regard to comorbidities, 243 patients (60.0%) had hypertension, 98 patients (24.2%) had diabetes mellitus, 29 patients (7.2%) had hyperlipidemia, 21 patients (5.2%) had anemia, and 25 patients (6.2%) had coronary artery disease. In addition, two patients (0.5%) were diagnosed with liver cirrhosis. There were 154 patients (38.0%) with a history of smoking and 38 patients (9.4%) with a history of alcoholism. The data on medication use were as follows: 43 patients (10.6%) had previously used anticoagulant drugs, 166 patients (41.0%) had previously used antiplatelet drugs, and 57 patients (14.1%) had previously used NSAIDs.

The primary and secondary outcomes are listed in *Table 2*. For all included patients, 1-year mortality was 5.4% (22 patients), 3-year mortality was 9.6% (39 patients), and 5-year mortality was 15.6% (63 patients). The incidence of stroke recurrence was 7.7% (31 patients). In total, 14 patients died in hospital and the mean length of hospital stay was 6.8±3.2 days.

Included patients were then divided into UGIB and

non-UGIB groups. Their clinical characteristics are listed in *Table 1*. Results showed that the mean age of the UGIB group was 61.5±9.6 years compared with 53.1±14.0 years in the non-UGIB group, and this difference was statistically significant (P<0.001). There were more male patients in the UGIB group (70.8%) than in the non-UGIB group (56.9%), however, this difference was not significant (P=0.065). The baseline NIHSS score was significantly higher in the UGIB group (11.3±2.3 points) than in the non-UGIB group (4.0±1.2 points) (P<0.001). Moreover, stroke subtypes were different between the two groups. There were more PACI patients in the UGIB group (P=0.041) and more TACI patients in the non-UGIB group (P=0.016). There were more patients with a prior history of anticoagulant drug use in the UGIB group (22.9%) than in the non-UGIB group (9.0%), and this difference was statistically significant (P=0.003). In regard to outcomes, AIS patients in the UGIB group had a higher 1-, 3-, and 5-year mortality rate, a higher incidence of stroke recurrence, a higher in-hospital mortality rate, and a longer length of hospital stay (all P<0.001) (*Table 2*).

The Kaplan-Meier curves of 5-year mortality and incidence of stroke recurrence are shown in *Figures 1* and *2*. Both curves show that AIS patients with UGIB had a higher 5-year mortality and a higher incidence of stroke recurrence than AIS patients without UGIB (both P<0.001 according to the log-rank test).

Results of the Cox proportional hazards analyses of the risk factors for 5-year mortality are shown in *Table 3*. Multivariate Cox regression indicated that the occurrence of UGIB, older age, a high NIHSS score, and stroke recurrence were related to a higher 5-year mortality rate. Univariate Cox regression indicated that hypertension may affect 5-year mortality. The risk factors for stroke recurrence are also shown in *Table 4*. Similar to the risk factors for 5-year mortality, the occurrence of UGIB, older age, a high NIHSS score, and hypertension were associated with an increase in the incidence of stroke recurrence according to the univariate Cox regression analysis.

Finally, predictors of UGIB in AIS patients are shown in *Table 5*. Older age, a high NIHSS score, and previous anticoagulant use were identified as predictors of UGIB in AIS patients according to the multivariate logistic regression analysis.

### Discussion

Previous studies have tended to focus on research

**Table 1** Clinical characteristics of total AIS patients, and AIS patients with and without UGIB

Variables	Total	UGIB	Non-UGIB	P value
n	405	48	357	
Age	54.1±13.8	61.5±9.6	53.1±14.0	<0.001
Gender, n (%)				0.065
Male	237 (58.5)	34 (70.8)	203 (56.9)	
Female	168 (41.5)	14 (29.2)	154 (43.1)	
Baseline NIHSS score	4.8±2.7	11.3±2.3	4.0±1.2	<0.001
Stroke subtype, n (%)				
PACI	133 (32.8)	22 (45.8)	111 (31.1)	0.041
TACI	99 (24.4)	5 (10.4)	94 (26.3)	0.016
LACI	100 (24.7)	10 (20.8)	90 (25.2)	0.509
POCI	73 (18.0)	11 (22.9)	62 (17.4)	0.348
Comorbidities, n (%)				
Hypertension	243 (60.0)	28 (58.3)	215 (60.2)	0.802
Diabetes mellitus	98 (24.2)	12 (25.0)	86 (24.1)	0.890
Hyperlipidemia	29 (7.2)	3 (6.3)	26 (7.3)	0.794
Anemia	21 (5.2)	3 (6.3)	18 (5.0)	0.723
Coronary artery disease	25 (6.2)	3 (6.3)	22 (6.2)	0.981
Liver cirrhosis	2 (0.5)	0 (0)	2 (0.6)	1.000
History of smoking, n (%)	154 (38.0)	15 (31.3)	139 (38.9)	0.303
History of alcoholism, n (%)	38 (9.4)	3 (6.3)	35 (9.8)	0.428
Previous anticoagulant use, n (%)	43 (10.6)	11 (22.9)	32 (9.0)	0.003
Previous antiplatelet use, n (%)	166 (41.0)	23 (47.9)	143 (40.0)	0.299
Previous NSAID use, n (%)	57 (14.1)	8 (16.7)	49 (13.7)	0.582

AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding; NIHSS, National Institute of Health Stroke Scale; PACI, partial anterior circulation infarct; TACI, total anterior circulation infarct; LACI, lacunar infarction; POCI, posterior circulation infarct; NSAID, non-steroidal anti-inflammatory drug.

concerning elderly AIS patients. However, research of middle-aged AIS patients is becoming more important considering the increased incidence of AIS in this category of patient. We included AIS patients aged from 40–65 years old, and the mean age of patients in our study was 54.1±13.8 years old. To our knowledge, this is also the first study investigating the relationship between UGIB and prognosis in AIS patients.

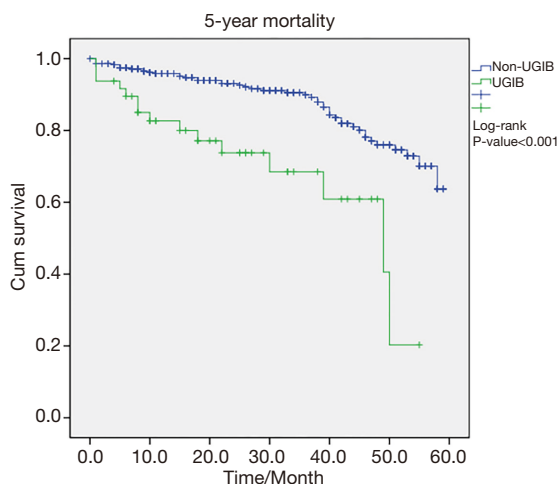
UGIB was verified as a significant risk factor for 5-year mortality in our study, which was similar to findings from previous studies of elderly patients (10,13). UGIB itself poses harm to patients, and can result in a mortality rate

of up to 16–24% (14–16). The harm to AIS patients is further magnified due to the poor condition of the patients themselves. Also, age has been verified as an independent risk factor for mortality in elderly AIS patients (17–19). In our study, older age remained an important risk factor for mortality in relatively younger AIS patients. NIHSS is a comprehensive scale of consciousness, limb movement, ataxia, balance and other aspects and represents the severity of stroke. The NIHSS score was verified in our study to be related to the increase in 5-year mortality. Previous studies found that initial impaired consciousness was related to an increase in the mortality of AIS patients (10). As impaired

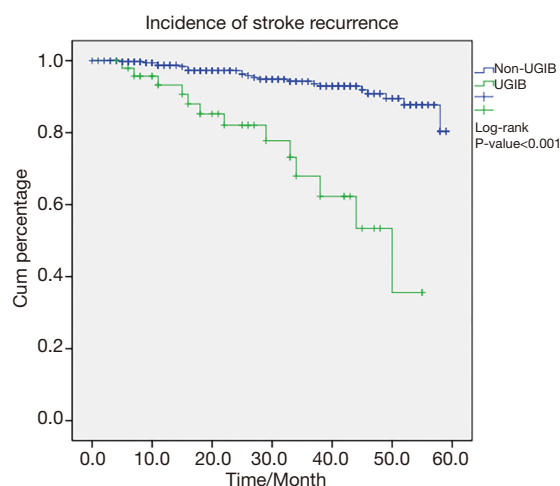
**Table 2** Outcomes of total AIS patients, and AIS patients with and without UGIB

Variables	Total	UGIB	Non-UGIB	P value
n	405	48	357	
Primary outcomes, n (%)				
1-year mortality	22 (5.4)	8 (16.7)	14 (3.9)	<0.001
3-year mortality	39 (9.6)	12 (25.0)	27 (7.7)	<0.001
5-year mortality	63 (15.6)	15 (31.3)	47 (13.2)	<0.001
Incidence of stroke recurrence	31 (7.7)	13 (27.1)	21 (5.9)	<0.001
Secondary outcomes				
In-hospital mortality, n (%)	14 (3.5)	3 (6.3)	5 (1.4)	<0.001
Length of hospital stay	6.8±3.2	13.5±3.1	5.9±1.9	<0.001

AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding.



**Figure 1** Kaplan-Meier curve of 5-year mortality between AIS patients with and without UGIB. AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding.



**Figure 2** Kaplan-Meier curve of stroke recurrence incidence between AIS patients with and without UGIB. AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding.

consciousness is only one item assessed by the NIHSS, we considered that the total NIHSS score was better than impaired consciousness alone in predicting the mortality of AIS patients. To some extent, stroke recurrence is also related to the severity of stroke. The recurrence of stroke was related to increased mortality in our study, and this was also found in previous studies (20,21).

Because of the effects of stroke recurrence on the mortality of AIS patients, we found that risk factors of stroke recurrence were similar to those of 5-year mortality, such as UGIB, older age, and a high NIHSS score. Du *et al.* found many risk factors of stroke recurrence in

their study including age, gender, NIHSS score, diabetes mellitus, coronary heart disease, and atrial fibrillation (11). Hypertension was also verified as an independent risk factor of stroke recurrence in their study, which is similar to our findings. This can be explained by the fact that long term hypertension can lead to arteriosclerosis and increased fragility, thus making stroke recurrence more likely.

Considering the importance of UGIB in the prognosis of AIS patients, the specific predictors of UGIB need to be identified. We found that older age, a high NIHSS score, and previous anticoagulant use were predictors of UGIB in AIS patients. Previous studies have also identified these

**Table 3** Cox proportional hazards regression analysis of 5-year mortality in AIS patients

Variables	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Occurrence of UGIB	3.394 (1.885–6.112)	<0.001	2.844 (1.568–5.158)	0.001
Older age	1.054 (1.031–1.078)	<0.001	1.033 (1.009–1.058)	0.008
High NIHSS score	1.231 (1.160–1.305)	<0.001	1.386 (1.191–1.612)	<0.001
Stroke recurrence	4.114 (2.030–8.338)	<0.001	3.481 (1.702–7.120)	0.001
Hypertension	3.659 (2.122–6.432)	0.012		

AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding; NIHSS, National Institute of Health Stroke Scale.

**Table 4** Cox proportional hazards regression analysis of recurrence in AIS patients

Variables	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Occurrence of UGIB	6.336 (3.125–12.845)	<0.001	2.929 (1.354–6.337)	0.006
Older age	1.060 (1.028–1.092)	<0.001	1.054 (1.023–1.086)	0.001
High NIHSS score	1.262 (1.177–1.354)	<0.001	1.221 (1.014–1.469)	0.035
Hypertension	4.801 (1.690–13.641)	0.003	3.793 (1.314–10.950)	0.014
Previous anticoagulant use	3.189 (1.056–9.641)	0.034		

AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding; NIHSS, National Institute of Health Stroke Scale.

**Table 5** Logistic regression analysis of predictors of UGIB in AIS patients

Variables	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Gender	1.842 (0.955–3.553)	0.068		
Older age	1.049 (1.024–1.075)	<0.001	1.055 (1.025–1.086)	<0.001
High NIHSS score	1.076 (1.033–1.120)	<0.001	1.085 (1.037–1.134)	<0.001
PACI	1.875 (1.019–3.453)	0.043		
TACI	0.325 (0.125–0.846)	0.021		
Previous anticoagulant use	3.019 (1.405–6.487)	0.005	2.556 (1.135–5.754)	0.023

AIS, acute ischemic stroke; UGIB, upper gastrointestinal bleeding; NIHSS, National Institute of Health Stroke Scale; PACI, partial anterior circulation infarct; TACI, total anterior circulation infarct.

three variables as predictors of UGIB (8,9,22). In addition, because hepatic cirrhosis is a coagulation disorder, it may also be related to the incidence of UGIB (8), but as only two patients in our study had cirrhosis this limited any further analysis. Stroke subtype may also affect the incidence of UGIB, however, the small population in our study limited the analysis of the relationship between stroke subtype and

the incidence of UGIB.

There are some limitations in our study. We included 405 AIS patients, but only 48 patients had UGIB. Considering the low incidence of UGIB in AIS patients, a larger sample size may be beneficial to further analyze the effect of UGIB on prognosis in AIS patients. Also, as this was a retrospective study and all data were collected



retrospectively, this may have led to some selection bias in our study which affected the results of the multivariate regression analysis. Moreover, we did not collect any data on the cause and treatment of UGIB, which may also be associated with the prognosis of AIS patients. Finally, detailed data concerning the dosage and duration of anticoagulant use, antiplatelet use, and NSAID use were not collected in this study, which may also be important factors affecting the incidence of UGIB.

## Conclusion

Our study found that AIS patients with UGIB had a higher 5-year mortality and a higher incidence of stroke recurrence than those without UGIB. Older age, a high NIHSS score, and previous anticoagulant use may be related to the incidence of UGIB in AIS patients. These results may provide some guidance for the treatment and nursing of AIS patients.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-21-907>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Affiliated Hospital of Jiangnan University (No.: 02019050). Written informed consent from patients was not required due to the retrospective nature of the study.

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