

A retrospective cohort study on the risk factors of gastrointestinal bleeding in acute ischemic stroke patients with atrial fibrillation

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ABSTRACT

Introduction. Gastrointestinal (GI) bleeding is a serious complication of stroke causing high morbidity. Atrial fibrillation is associated with both ischemic stroke and GI bleeding due to usage of anticoagulant. The aim of this study is to determine the risk factors of GI bleeding in ischemic stroke patients with atrial fibrillation.

Material and methods. All ischemic stroke patients with atrial fibrillation from January 2017 to December 2018 were extracted from our hospital-based stroke registry. We extracted demographical characteristic, subtypes of stroke, and medication history.

Results. We found 96 ischemic stroke patients with AF were included in the study. Dyslipidemia (RR: 0.2; 95%CI: 0.043-0.939; $p = 0.049$) and antihyperlipidemic drugs (RR: 0.183; 95%CI: 0.039-0.857; $p = 0.022$) was associated with lower GI bleeding risk. There were no significant association between other risk factors and GI bleeding incidence

Conclusion. Our research shows that dyslipidemia and history of antihyperlipidemic drugs are associated with lower GI bleeding risk in ischemic stroke patients with AF.

Keywords: atrial fibrillation, dyslipidemia, gastrointestinal bleeding, ischemic stroke

INTRODUCTION

Gastrointestinal (GI) bleeding is one of the systemic complications of stroke which causes high morbidity (1,2). The incidence of GI bleeding after acute ischemic stroke ranges from 0.1% to 8.0% (1,3,4). Patients who had GI bleeding outcome after stroke were reported to have poorer clinical outcome, including neurologic deterioration, in-hospital mortality, and poor functional outcome (3,5). The incidence of GI bleeding in stroke patients are often also increased due to administration of anticoagulation treatment (6).

Atrial fibrillation, which is a well-known risk factor for ischemic stroke, coincidentally also poses a high risk of GI bleeding (7,8). In these patients, the most common risk for gastrointestinal

bleeding was the use of anticoagulation treatment (9,10). The occurrence of gastrointestinal bleeding can affect ischemic stroke and atrial fibrillation therapy, such as the decision to administer antiplatelet and anticoagulants, ultimately affecting the patient's prognosis. In addition to those drugs, administration of other medications such as NSAID and steroid also contributes to the development of GI bleeding (1). Previous studies have evaluated risk factors for GI bleeding in stroke. However, data on GI bleeding risk in patients with ischemic stroke and AF are still limited. As both diseases are often treated with antiplatelet and anticoagulants, it is possible that patients with both diseases are at higher risk of GI bleeding. Therefore, this study aims to determine the risk factors

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Article History:

Received: 19 April 2021

Accepted: 19 June 2021

of GI bleeding in ischemic stroke patients with atrial fibrillation.

MATERIAL AND METHODS

Data from our hospital-based stroke registry were used in this population-based retrospective cohort study. The institutional review and ethics board had reviewed and approved the study protocol. The Stroke Registry prospectively registered all patients who had stroke and were hospitalized for 7 days after the stroke onset in participating hospitals. We defined ischemic stroke as a sudden onset of non-convulsive, focal neurological deficit confirmed by either computed tomography and/or magnetic resonance imaging for brain.

All patients admitted between January 2017 to December 2018 with ischemic stroke and/or transient ischemic attack who were hospitalized within 7 days of stroke onset were included. From these patients, we exclude registry with incomplete data, patients who are transferred to another hospital, and patients requesting discharge against medical advice. We retrospectively reviewed this dataset and classify ischemic stroke into cardioembolic and noncardioembolic subtypes (i.e., small vessel, large vessel, and unclassified).

Demographical characteristic such as gender, age, and types of antithrombotic agent used were collected on admission or during hospitalization. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg, diastolic blood pressure (DBP) ≥ 90 mm Hg or history of treatment with antihypertensive drugs. Dyslipidemia was defined as serum low-density lipoprotein (LDL) level ≥ 100 mg/dl, high-density lipoprotein (HDL) level < 45 mg/dl, triglycerides ≥ 150 mg/dl mmol/l, or history of treatment with a cholesterol-lowering drug. Hypoalbuminemia defined as albuminemia level < 3.5 g/dl. Diabetes and liver failure were diagnosed based on diagnostic criteria of Indonesian Internist Society or medical history of diabetes and liver failure.

Any medication history such as anti-thrombotic, analgesic, anticonvulsant, antihyperlipidemic, antiarrhythmic, antidepressant, antibiotic, antifungal, antiepileptic, allopurinol, PPI, and vitamin C were also recorded. Atrial fibrillation was diagnosed based on electrocardiographic examination on admission and during hospitalization, or previ-

ous history of atrial fibrillation. GI bleeding was defined as any episode of hematemesis or melena during hospitalization.

Established risk factors for GI bleeding, including age 65 or older; concomitant acetyl salicylic acid (ASA), corticosteroid, or anticoagulant usage; previous history of ulcers, ulcer bleeding, or dyspepsia; the use of two NSAIDs or maximum dose recommended of one NSAID. We classified patients into three GI bleeding risk categories. Patients without any of the clinical conditions mentioned were classified as low risk. Subjects with at least one of age 65 or older, concomitant use of low-dose ASA or corticosteroids, history of symptomatic peptic ulcer, history of dyspepsia, current usage of maximum dose NSAID and current use of two NSAIDs were classified as intermediate risk. Patients who had one of the following conditions – GI bleeding history, concomitant use of NSAIDs and anticoagulants, or the presence of three risk factors described for intermediate GI bleeding risk – were defined as high risk.

Chi-square test was used to analyze factors associated with GI bleeding. Variables with p value of < 0.05 were then included in the multivariate analysis for GI bleeding risk factors. Multivariate analysis was conducted using logistic regression. Adjusted risk ratio (RR) were calculated, controlling for multiple confounding factors including age, gender, onset of stroke, comorbidities, bleeding risk and medication history. Data were analyzed using SPSS version 21.0 (IBM SPSS, Somers, N.Y., USA). This study has been reviewed and approved by our Ethical Committee.

RESULTS

About 96 ischemic stroke patients with atrial fibrillation were included in the study. Table 1 shows the baseline characteristic and demographic of patients. Most of the patients were aged more than 60 years old (91.7%). Most patients (72.9%) arrived within 24 hours of stroke onset. 53 (55.2%) subjects were male and 43 (44.8%) were female. More than half of the study subjects had hypertension (65.6%) and dyslipidemia (62.5%). Among all the patients, the most used antithrombotic was Clopidogrel (37.5%), Aspirin (35.4%), followed by warfarin (10.4%) and Aspirin+Clopidogrel combination therapy (10.4%). Characteristics of

patients included in the study are presented in Table 1.

TABLE 1. Demographic profile of the study subjects

Subject characteristics		n (%)
Gender	Male	53 (55.2)
	Female	43 (44.8)
Age (years)	> 60	88 (91.7)
	≤ 60	8 (8.3)
Onset period (hours)	> 24	26 (27.1)
	≤ 24	70 (72.9)
Type of antithrombotic	Warfarin	10 (10.4)
	Dabigatran	2 (2.1)
	Rivaroxaban	2 (2.1)
	Clopidogrel	36 (37.5)
	Aspirin	34 (35.4)
	Aspirin+Clopidogrel	10 (10.4)
	Cilostazol	2 (2.1)
Comorbidities		
Hypertension	Yes	63 (65.6)
	No	33 (34.4)
Dyslipidemia	Yes	60 (62.5)
	No	36 (37.5)
Liver failure	Yes	0 (0)
	No	96 (100)
Diabetes mellitus	Yes	21 (21.9)
	No	75 (78.1)
Hemorrhage history	Yes	1 (1)
	No	95 (99)
Hypoalbuminemia	Yes	5 (5.2)
	No	91 (94.8)

Compared with patients who did not have GI bleeding, patients with GI bleeding were more often male (13.2% vs. 2.3%) and arrived at hospital within 24 hour of stroke onset. However, this difference was not statistically significant ($p = 0.071$). All patients who had GI bleeding were aged more than 60 years old. There was no difference in the prevalence of hypertension in the GI bleeding group compared to control (11.1% vs. 3%; $p = 0.256$). There was also no significant difference in the prevalence of diabetes in both groups (4.7% vs. 9.3%; $p = 0.681$). However, there were significant difference in proportion of patients with dyslipidemia, with the GI bleeding group having lower dyslipidemia comorbidity (OR: 0.200; CI 95%: 0.043-0.939; $p = 0.049$). In our study, more often patients received anti hyperlipidemic (64,6%) as concomitant therapy. Apparently, therapy using these agents is significantly associated with lower risk of GI bleeding (OR: 0.183; CI 95%: 0.039-0.857). Patients with GI bleeding in the trial were more likely to have had a history of receiving aspirin, clopidogrel and cilostazol medication. Interestingly, different types of antithrombotic drug is

not associated with increased GI bleeding risk. Table 2 contains the detailed information on bivariate analysis performed.

After multivariate adjustment, patients with dyslipidemia and patients receiving antihyperlipidemic treatment were not independent predictive factors of GI bleeding in ischemic stroke patients with atrial fibrillation (Table 4).

When stratified by bleeding risk, patients with low bleeding risk suffered higher GI bleeding compared with patients who had intermediate or high risk of bleeding. However, this difference was not statistically significant ($p > 0.05$; Table 3).

DISCUSSION

The present study aims to find out whether there is association between GI bleeding and ischemic stroke in patients with atrial fibrillation. The result of our study shows that in stroke patients, most subjects were male. This is in accordance to the study by Son et al. (11), showing that the prevalence of ischemic stroke with atrial fibrillation is higher in men compared to women. However, other study also stated that the risk of atrial fibrillation is higher in women compared to men (12). A study by Alkhouli et al. (13). shows that the incidence of ischemic stroke is higher in women compared to men. The author argued that this is because women is at higher risk of atrial fibrillation. The difference of incidence in this research might be attributed to different patient characteristics and small sample size.

Most of our study subjects are aged above 60 years old. We argue that patient with age older than 60 years old tend to have higher risk of ischemic stroke with atrial fibrillation. This result is in accordance to the research by Yang et al. (14), involving 305 patients with stroke ischemic and atrial fibrillation. The result of the study shows that the average age of the subjects was older than 72 years old, and the incidence is higher in men compared to women. It has been researched before that age older than 75 years old is one of the main risk factor for ischemic stroke and atrial fibrillation (11,15,16).

In our study, the most prevalent comorbidities were hypertension. This result is in accordance by the research by Alkhouli et al. (13), showing that more than half of ischemic stroke and atrial fibril-

TABLE 2. Bivariate analysis of risk factors associated with gastrointestinal bleeding

Risk factors	GI bleeding				RR	95% CI	p
	Yes		No				
	n	%	n	%			
Gender							
Male	7	87.5	46	52.3	5.679	0.727-44.395	0.071*
Female	1	12.5	42	47.7			
Age							
> 60	8	9.1	80	90.9	-	-	-
≤ 60	0	0	8	100.0			
Onset period							
> 24	3	11.5	23	88.5	1.615	0.415-6.286	0.679*
< 24	5	7.1	65	92.9			
Type of antithrombotic							
Warfarin	0	0	10	100.0	-	-	-
Dabigatran	0	0	2	100.0	-	-	-
Rivaroxaban	0	0	2	100.0	-	-	-
Clopidogrel	5	13.9	31	86.1	0.278	0.056-1.385	0.294*
Aspirin	2	5.9	32	94.1	0.118	0.017-0.811	0.162*
Aspirin+Clopidogrel	0	0	10	100.0	-	-	-
Cilostazol	1	50.0	1	50.0	Ref		
Comorbidity							
Hypertension							
Yes	7	87.5	56	63.6	3.667	0.471-28.554	0.256*
No	1	12.5	32	36.4			
Dyslipidemia							
Yes	2	25.0	58	65.9	0.200	0.043-0.939	0.049*
No	6	75.0	30	34.1			
Diabetes Mellitus							
Yes	1	12.5	20	22.7	0.510	0.066-3.918	0.681*
No	7	87.5	68	77.3			
Co-medication							
Analgesic							
Yes	1	12.5	7	8.0	1.571	0.220-11.227	0.515*
No	7	87.5	81	92.0			
Anticonvulsant							
Yes	0	0	9	10.2	-	-	-
No	8	100.0	79	89.8			
Antihyperlipidemic							
Yes	2	25.0	60	68.2	0.183	0.039-0.857	0.022*
No	6	75.0	28	31.8			
Antiarrhythmic							
Yes	4	50.0	22	25.0	2.692	0.726-9.986	0.206*
No	4	50.0	66	75.0			
Antidepressant							
Yes	0	0	3	3.4	-	-	-
No	8	100.0	85	96.6			
Antibiotic							
Yes	0	0	3	3.4	-	-	-
No	8	100.0	85	96.6			
Antifungal							
Yes	1	12.5	0	0	13.571	6.652-27.687	0.083*
No	7	87.5	88	100.0			
Antiepileptic							
Yes	0	0	12	13.6	-	-	-
No	8	100.0	76	86.4			
Allopurinol							
Yes	0	0	1	1.1	-	-	-
No	8	100.0	87	98.9			
PPI							
Yes	1	12.5	6	6.8	1.816	0.259-12.753	0.467*
No	7	87.5	82	93.2			
Vitamin C							
Yes	1	12.5	0	0	13.571	6.652-27.687	0.083*
No	7	87.5	88	100.0			

*Chi-square test

TABLE 3. Stratification of GI bleeding event according to bleeding risk

Bleeding risk	GI bleeding				RR	95% CI	p
	Yes		No				
	n	%	n	%			
Low	6	7.4	75	92.6	Ref		
Intermediate	1	20.0	4	80.0	0.370	0.055-2.531	0.353*
High	1	10.0	9	90.0	0.741	0.099-5.542	0.570*

*Chi-square test

TABLE 4. Multivariate analysis of risk factors associated with gastrointestinal bleeding

Risk factors	RR	95% CI	p*
Dyslipidemia	0.488	0.030-7.969	0.614
Antihyperlipidemic	0.280	0.017-4.556	0.371

*Logistic regression test

lation patients have a history of hypertension. Son et al. (11) also reported that hypertension was the strongest risk factor in patients with atrial fibrillation, with hypertensive patient having 2.7 times the risk of developing atrial fibrillation compared to control. Additionally, diabetic patients were at 1.6 times risk of developing stroke with atrial fibrillation. In our result, history of dyslipidemia and were found to be a risk of ischemic stroke in patients with AF. Several researches shows that atherosclerosis is a predictor of ischemic stroke in AF patients, and subsequently dyslipidemia as it is one of the risk factor of atherosclerosis. However, the association between dyslipidemia, AF and stroke are poorly understood. Previous research shows that total cholesterol and LDL is associated with increased risk of ischemic stroke in AF patients (15).

Our research shows higher incidence of GI bleeding in men compared to women. This is in accordance to research by Ji et al. (2), showing that men have higher risk of GI bleeding in ischemic stroke compared to women. All patients with GI bleeding in this research is aged > 60 years old. We argue that this is because physiological function in older age is already deteriorating, including the gastrointestinal system and therefore older population is more prone to GI bleeding. This is in accordance to the previous study showing that most patients with GI bleeding after stroke is aged > 65 years old (17).

The risk of GI bleeding in elderly is also associated with antithrombotic treatment, especially in atrial fibrillation (18). In our research, most patients with GI bleeding have history of antithrom-

botic treatment such as aspirin, clopidogrel, and cilostazol. This is in accordance to previous studies showing that most GI bleeding patients have some history of antithrombotic treatment (3,19).

Interestingly, dyslipidemia was a protective factor towards GI bleeding. This phenomenon was also observed by Ogata et al. (3), although the exact mechanism of which this phenomenon can happen is still unknown. One possible reason is that one of the cause for GI bleeding is *Helicobacter pylori* infection. This infection will increase proinflammatory cytokines such as CRP, IL-6 and IL-8 which will increase fat metabolism, subsequently causing dyslipidemia (20-22). Other studies also shows that eradication of *H. pylori* is associated with increased BMI and increased incidence of dyslipidemia. This can be caused due to the subjective symptoms of functional dyspepsia in the patient being lessened, therefore increasing the patients' appetite and quality of life (23,24). This subsequently contributes to increased weight gain and dyslipidemia. However, further research on the association between dyslipidemia and GI bleeding should be conducted. Our research do not include the source and cause of GI bleeding. Furthermore, we do not sought past *H. pylori* infection and medication for its eradication. Therefore we cannot determine whether dyslipidemia is associated with *H. pylori* infection. Additionally, it is possible that the numbers in our research is skewed due to many patients already taking antihyperlipidemic drugs and therefore their blood cholesterol level is in the normal range. Therefore, further research involving larger sample size is warranted.

More than half of the patients in our research have taken antihyperlipidemic drugs as adjuvant therapy. Our research shows that antihyperlipidemic drug therapy is associated with lower GI bleeding incidence. This is in accordance to other researches showing that antihyperlipidemic drugs, especially statins, are associated with lower bleeding risk (25). Although another research shows increased bleeding risk (26) and no significant association with bleeding risk (27). Statin is known to increase cyclooxygenase-2 gene expression and release of PGE₂ in the stomach. Prostaglandins are known to be protective towards gastric mucosa and may reduce gastric bleeding risk. Therefore, administration of statins in adjunction to anticoagulants may reduce risk of gastric bleeding (26).

Previous studies show that warfarin and statin combination therapy can reduce gastric bleeding risk caused by warfarin. This is because statin is a competitive inhibitor of the enzyme CYP29, which metabolizes warfarin (28). However, other study found out that statin therapy increased the risk of gastric bleeding (26). The difference in these result might be due to different types of antithrombotic, duration of therapy, drug interaction, and other risk factors. Therefore, additional data on the effect of antihyperlipidemic drugs on gastric bleeding risk is required before definitive conclusion can be drawn.

After multivariate analysis, dyslipidemia and antihyperlipidemic therapy were not significantly associated with GI bleeding in ischemic stroke patients with AF. This is because there are various factors affecting GI bleeding including dose and length of medication, types of antihyperlipidemic agents, combination therapy, comorbidities, and the types of GI bleeding itself.

The main side effect of antithrombotic drugs is GI bleeding. Long-term effect of antithrombotic can increase risk of GI bleeding, especially in the elderly (16,29,30). This is not in accordance to our result showing that usage of antithrombotic is not significantly associated with GI bleeding. We argued that this might be caused by many factors affecting the incidence of GI bleeding including dose, length of medication, combination with other drugs such as NSAID or oral anticoagulant, and history of GI bleeding. In this study, we do not collect data on those variables and therefore we can-

not determine the exact relationship.

One main factor of GI bleeding is the existing pathology (e.g. mucosal atrophy), old age, renal dysfunction, history of bleeding, long term usage of antithrombotic, and long term usage of aspirin in any dose. Previous study shows that 300 mg of aspirin increases risk of bleeding by twofold compared to 100 mg aspirin (31). The risk of dual therapy of aspirin and clopidogrel (CPG) increases risk of bleeding by 1.3% after 30 days of usage. Past case-control study shows that GI bleeding risk in low dose aspirin is 3.7-fold, in CPG 2.8-fold, and in CPG+Aspirin is 16.4-fold. Usage of NSAID also increased risk of bleeding (31-33).

In this research, subjects are classified as low risk, medium risk, and high risk depending on their risk factors such as age older than 65 years, usage of ASA, corticosteroid, and anticoagulant, history of ulcer, bleeding or dyspepsia, and usage of NSAID. Our research shows that there is no association between high bleeding risk and the incidence of GI bleeding. Previous research shows that patient with history of disease and usage of drugs has higher risk of GI bleeding (5,21,23). This might be caused by the low sample of this research.

This research is not without limitations. Firstly, the low sample size compared to previous research might mask any significant association between the variables. Secondly, the duration of treatment and the dose is not recorded, which may increase risk of bleeding. Additionally, gastroprotective drugs such as PPI is not recorded in this research, which may affect the incidence of GI bleeding.

CONCLUSIONS

The present research aims to determine the risk of GI bleeding in ischemic stroke patients with AF. Our result shows that dyslipidemia and history of antidyslipidemic drugs are associated with lower GI bleeding risk, while there were no other significant risk factors associated with GI bleeding. Further research involving large samples are warranted to increase the power of research.

Acknowledgement

All authors have equal parts in doing this article.

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Conflict of interest: none declared
Financial support: none declared