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RESEARCH ARTICLE

Predicting factor analysis of gastrointestinal bleeding complication among hospitalised ischemic stroke patients

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Abstract

Background: Stroke is a common cardiovascular disease and the biggest cause of death and disability in the world. Treatment in affected patients aims to stabilise their condition and prevent further deterioration. One of the therapies in stroke patients is the administration of antiplatelet which may also cause adverse reactions in the form of gastrointestinal bleeding. **Objectives:** This study aims to analyse the factors that can predict the emergence of gastrointestinal bleeding in hospitalised Ischemic stroke patients. **Methods:** A cohort study was conducted within a population of hospitalised patients diagnosed with Ischemic stroke. Patients' data from the hospital stroke registry was analysed. The significance of factors that can predict gastrointestinal bleeding incidence and the main predictor was determined. **Results:** The results showed that out of the 96 patients included, 49 experienced gastrointestinal bleeding. Factors that had significant relationships with the incidence of gastrointestinal bleeding were symptoms of decreased consciousness with OR 9.03; 95% CI: 3.361 – 24.22, and loading dose OR 5.769; 95% CI: 1.191 – 27.941. In addition, the main predicting factor was symptoms of decreased consciousness with a $p < 0.05$ (<0.010), and OR value of 2.165 with 95% CI: 3.177 – 23.906. **Conclusion:** The occurrence of decreased consciousness can be a predictor of gastrointestinal bleeding.

Introduction

Stroke is a clinical syndrome characterised by acute or sudden attacks and leads to persistent paralysis of one side or the whole body (Chisholm-Burns *et al*., 2016). It is a common cardiovascular disease, as well as the biggest cause of death and disability worldwide (Venketasubramanian *et al*., 2017). The global prevalence in 2019 was 101.5 million cases, out of which ischemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage were 77.2 million, 20.7 million, and 8.4 million, respectively (AHA, 2021). Overall, in 2019, stroke was more prevalent in Oceania, Southeast Asia, North Africa, the Middle East, and East Asia (AHA, 2021). Furthermore, as stated in the year 2018 report of the Riskesdas data (KemenkesRI, 2019), the prevalence according to doctors' diagnoses in those aged 15 years was 10.9% or 2,120,362 in the total Indonesian population. The provinces with the highest prevalence of stroke were East Kalimantan (14.7%) and the special region of Yogyakarta (14.6%) (KemenkesRI, 2019).

Ischemic stroke is the most common type (AHA, 2021), accounting for approximately 85% of cases, while the other 15% are attributed to intracerebral haemorrhage. The treatment goal of short-term stroke management is to minimise secondary brain injury by rebuilding and maintaining perfusion to the affected area, protecting nerve cells, and maximising patient recovery (Chisholm-Burns *et al*., 2016). Meanwhile, the long-term goal of acute ischemic stroke is to prevent recurrent conditions by reducing and modifying risk factors using appropriate therapy (Chisholm-Burns *et al*., 2016). Therapeutic options in the treatment include alteplase, antiplatelet, and anti-coagulant (Powers *et al*., 2019). The most commonly used therapy for ischemic stroke management is antiplatelet therapy. Antiplatelet drugs are known to have good efficacy in the treatment and prevention of recurrent stroke (Hackam & Spence, 2019).

However, apart from their good efficacy, antiplatelet drugs also have side effects; in low-dose aspirin users, upper gastrointestinal symptoms are common, such as chest pain and dyspepsia, which occur in 15-20% of patients (Lanas & Gargallo, 2015). Major haemorrhage requiring blood transfusion reportedly occurred in 0.9% of patients receiving clopidogrel (75 mg/day) plus aspirin in a dose range of 50-325 mg/day, as well as 0.4% in those receiving aspirin alone (Johnston *et al.*, 2018).

Predicting the incidence of gastrointestinal bleeding in stroke patients is important as a preventive measure. This is because the occurrence of gastrointestinal bleeding is associated with a high risk of death, and causes the patients to lose their freedom (Du *et al*., 2020). Therefore, this study aims to analyse the predicting factors for the occurrence of gastrointestinal bleeding among ischemic stroke patients during hospitalisation.

Methods

Design

This is a cohort study with data collection through the hospital stroke patients' data registry. The population were patients diagnosed with ischemic stroke and being hospitalised during the study period. The inclusion criteria were: patients aged over 18 years diagnosed with ischemic stroke; those receiving antiplatelet drugs at the study site. Meanwhile, the exclusion criteria were: patients who were pregnant and breastfeeding, as well as those using long-term non-steroidal anti-inflammatory drugs (OAINS).

Ethics approval of this study was obtained from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada – Dr Sardjito General Hospital with approval number KE/FK/0674/EC/2022.

Assessment

The primary factor used for assessment in this study was gastrointestinal bleeding, which is defined as the occurrence of haematemesis or melena during hospitalisation (Ogata *et al*. 2014). The decreased consciousness was also assessed using the Glasgow Coma Scale (GSC). The data collected include patient demographics, comprising gender and age; stroke data, such as type of recurrence and symptoms of decreased consciousness; drug use data such as hypertension and diabetes therapy; as well as antiplatelet use.

Data analysis

The data obtained were analysed descriptively to determine the distribution of stroke patients in this study. The significance of the relationship between the predictor factors and the incidence of gastrointestinal bleeding was analysed by chi-square. Predictor factors that have significant relationships were then analysed using multivariate logistic regression to identify the main predictors.

Results

The distribution of ischemic stroke patients' characteristics, based on the incidence of gastrointestinal bleeding, is presented in Table I. The basic characteristics include demographics, diagnoses, and treatments. Ethics approval of this study was obtained from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada – Dr Sardjito General Hospital with approval number KE/FK/0674/EC/2022. In total, 96 patients' data were accessed and then used for this study. Exactly 49 patients experienced gastrointestinal bleeding, while 47 had no gastrointestinal bleeding experience. The results showed that among the patients who experienced gastrointestinal bleeding (n=49), 77.6% (n=38) were aged 60 years, while 69.4% (n=34) were males. Similarly, 63.3% (n=31) of patients were newly diagnosed with stroke, and 61.2% of the patients (n=30) presented symptoms of decreased consciousness.

In addition, the characteristics of the treatments received by all 96 patients were also analysed. The results showed that 15.6% (n=15) and 11.4% (n=11) of patients with hypertension and diabetes therapy,

respectively, experienced gastrointestinal bleeding. Furthermore, the antiplatelet regimen with the highest incidence was dual therapy at 39.6% and without loading dose at 40.6%. The distribution of patients' characteristics based on the incidence of gastrointestinal bleeding is shown in Table I.

Table I: Distribution of ischemic stroke patient characteristics based on the incidence of gastrointestinal bleeding during hospitalisation

Patients' characteristics		Gastrointestinal bleeding		Total (n=96)	Number of gastrointestinal bleeding		Total (n=96)	Total
		N	%	%	N	%	%	N (%)
Age (years old)	< 60	11	22.5	11.5	12	25.5	12.5	23 (24.0)
	≥ 60	38	77.6	39.6	35	74.5	36.4	73 (76.0)
Gender	Male	34	69.4	35.4	29	61.7	30.2	63 (65.6)
	Female	15	30.6	15.6	18	38.3	18.8	33 (34.4)
Stroke diagnosed	Newly diagnosed	31	63.3	32.3	29	61.7	20.2	60 (62.5)
	Repeated stroke	18	36.7	18.8	18	38.3	18.75	36 (37.5)
Symptoms of loss of consciousness	Yes	30	61.2	31.2	7	14.9	7.3	37 (38.5)
	No	19	38.8	19.8	40	85.1	41.7	59 (61.5)
Hypertension therapy	Yes	15	30.6	15.6	12	25.5	12.5	27 (28.1)
	No	34	69.4	35.4	35	74.5	36.5	69 (71.9)
Diabetes Mellitus therapy	Yes	11	22.5	11.4	9	19.1	9.4	20 (20.8)
	No	38	77.6	39.6	38	80.9	39.6	76 (79.2)
Antiplatelet treatment regimen	Single	11	22.5	11.4	12	25.5	12.5	23 (24.0)
	Combination	38	77.6	39.6	35	74.5	36.4	73 (76.0)
Loading dose	Yes	10	20.4	10.4	2	4.3	2.1	12 (12.5)
	No	39	80.6	40.6	45	95.7	46.9	84 (87.5)

The characteristics were analysed using the chi-square test to determine the significance of their relationship with the incidence of gastrointestinal bleeding. The results showed that characteristics having significant associations with the incidence of gastrointestinal bleeding include symptoms of decreased consciousness OR 9.03; 95% CI: 3.361 – 24.22, and loading dose OR 5.769; 95% CI: 1.191 – 27.941. Details of the relationship between risk factors and the incidence of gastrointestinal bleeding are presented in Table II. Furthermore, the multivariate logistic regression analysis results in Table III showed that the main predictor variable was a loss of consciousness with a $p<0.05$ ($p<0.010$) and OR value of 2.165 (95% CI: 3.177 – 23.906).

Table II: The relationship of risk factors with the incidence of gastrointestinal bleeding in stroke patients

Patients' characteristics		Gastrointestinal bleeding	No Gastrointestinal bleeding	OR	CI (95%)	*p*
Age (years old)	< 60	11	12	0.844	0.33	0.454
	≥ 60	38	35		2.157	
Gender	Male	34	29	1.407	0.604	0.282
	Female	15	18		3.277	
Stroke diagnosed	Newly diagnosed	31	29	1.069	0.468	0.521
	Repeated stroke	18	18		2.443	
Symptoms of loss of consciousness	Yes	30	7	9.023	3.361	**0**
	No	19	40		24.22	
Hypertension therapy	Yes	15	12	1.287	0.526	0.653
	No	34	35		3.146	
Diabetes therapy	Yes	11	9	1.222	0.455	0.442
	No	38	38		3.286	
Antiplatelet treatment regimen	Single	11	12	0.844	0.33	0.454
	Combination	38	35		2.157	
Loading dose	Yes	10	2	5.769	1.191	0.017
	No	39	45		27.941	

Table III: Multivariate logistic regression test results

Variable	OR	CI (95%)	*p*
Age	-0.19	0.278 -2.462	0.733
Loading dose	1.615	0.915 - 27.623	0.063
Symptoms of loss of consciousness	2.165	3.177 - 23.906	<0.010

Discussion

The incidence of stroke, which is mostly attributed to sudden blockage of the arteries in the brain, is usually caused by the occurrence of blood clots. Treatment by administering antiplatelets such as aspirin can prevent the formation of new clots, thereby speeding up recovery after a stroke (Sandercock *et al*., 2014).

Overall, aspirin reduced the risk of serious vascular events by 19% (7%-25%), non-fatal myocardial infarction by 36% (15%-52%), major coronary events by 21% (5%–34%), and each stroke by 17% (, 4%–28%). The odds of ischemic and definite ischemic stroke were both significantly reduced at 22% and 21%, respectively. In contrast, haemorrhagic stroke and gastrointestinal bleeding with a relative risk of 1.90; 1.06–3.44 and 2.69; 1.25–5.76, respectively, were elevated (Hackam & Spence, 2019).

Apart from its effectiveness in the management of stroke, antiplatelets can also cause gastrointestinal disturbances (Lanas & Gargallo, 2015). Low-dose aspirin potentially causes upper gastrointestinal disorders, ranging from symptoms -without- lesions to severe complications such as peptic ulcer bleeding and even death (Lanas & Gargallo, 2015). Upper gastrointestinal symptoms in patients with low doses are common, including heartburn and dyspepsia, as well as epigastric discomfort, bloating, and early satiety, which occur in 15-20% of patients (Lanas & Gargallo, 2015). In this study, the antiplatelet agents used were aspirin and clopidogrel, and both were used in single and multiple administrations. In the administration, some patients were given a loading dose, while others were not.

Age and gender are non-modifiable risk factors for stroke ((Allen & Bayraktutan, 2008; Boehme *et al*., 2017; Fekadu *et al*., 2019; Parmar, 2018). Increasing age elevates the incidence of stroke by doubling every decade after the age of 55 (Allen & Bayraktutan, 2008; Boehme *et al*., 2017; Fekadu *et al.*, 2019; Parmar, 2018). The relationship between sex and the risk of stroke depends on age. At a young age, females have higher risks of stroke than their male counterparts, although, at older ages, the relative risk is slightly higher for males (Allen & Bayraktutan, 2008; Boehme *et al.*, 2017; Fu, 2019; Parmar, 2018). Besides becoming risk factors for stroke, some studies showed that males and humans of older ages also mostly experienced gastrointestinal bleeding (Fu, 2019; Ogata *et al*., 2014). The results of this study showed that patients who mostly experienced gastrointestinal bleeding were males and aged over 60 years, but this was not significant. This result is consistent with previous studies (Fu, 2019; Ogata *et al*., 2014).

Regarding the frequency of gastrointestinal bleeding based on the diagnoses of stroke, 31 (32.3%) patients were newly diagnosed with a stroke, and based on stroke symptoms, 30 (31.2%) patients had decreased consciousness. The relationship between the patients' stroke diagnosis status and the incidence of gastrointestinal bleeding was not significant. Meanwhile, loss of consciousness was significantly related to the incidence of gastrointestinal bleeding.

In terms of antiplatelet therapy, patients with multiple therapy regimens, such as a combination of 2 antiplatelets and those without loading doses, had high incidences of gastrointestinal bleeding with values of 38 (39.6%) and 39 (40.6%), respectively. In this study, the most widely used antiplatelet combination was a combination of clopidogrel and aspirin/acetylsalicylic acid. A combination of clopidogrel and aspirin may reduce stroke recurrence (Johnston *et al*., 2018). However, the use of antiplatelet combinations can also increase the risk of gastrointestinal bleeding (Johnston *et al*., 2018; Vallurupalli & Goldhaber, 2006). The loading dose of clopidogrel in this study was 300 mg, followed by a maintenance dose of 75 mg, following the guidelines for the management of Acute Ischemic Stroke (Powers *et al*., 2019).

Based on the results, decreased consciousness and loading dose of clopidogrel were factors significantly associated with the incidence of gastrointestinal bleeding. Meanwhile, the main predictor factor is a loss of consciousness.

Conclusion

The predictor factors that had significant relationships with the occurrence of gastrointestinal bleeding were symptoms of decreased consciousness and loading

dose. Meanwhile, the main predictor was the symptom of decreased consciousness. This indicates that antiplatelet administration needs to be monitored closely in patients with symptoms of decreased consciousness.

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