Some risk factors for recurrent ischemic stroke caused by middle cerebral artery damage

Nguyen Thi Huyen[1✉], Phan Van Duc[2], Nguyen Thanh Binh[1,3]

[1] Ha Noi Medical University
[2] Neurology Center – Bach Mai Hospital
[3] Department of Neurology and Alzheimer Disease – National Geriatric Hospital

Correspondence to

Nguyen Thi Huyen
Hanoi Medical University

ABSTRACT

Background and Purpose: Recurrent ischemic stroke due to damage to the middle cerebral artery causes deterioration of neurological function and increases the rate of disability, death, and treatment costs many times compared to the first ischemic stroke. Assessing risk factors plays an extremely important role in preventing recurrent ischemic stroke. We have discuss some risk factors for recurrent ischemic stroke caused by middle cerebral artery damage.

Research subjects and methods: Cross-sectional descriptive study on 77 patients with recurrent ischemic stroke due to middle cerebral artery damage at the Neurology Center - Bach Mai Hospital from July 2021 to August 2022.

Summary of review: There were 22 female patients and 55 male patients with an average age of 65 ± 11 years old, predominantly in the age group of 61 - 70 years old (making up 44,2% of the total). The majority of patients experienced their first recurrence (64,9%). The timeframe between the most recent ischemic stroke and the recurrent event ranged from 12 months to 5 years, with the highest occurrence rate at 33,8%. Hypertension has the highest rate among risk factors (88,3%); Hyperlipidemia follows as the second leading risk factor (49,4%). Patients with recurrent ischemic stroke caused by middle cerebral artery damage showed limited effectiveness in recurrence prevention treatment: 68.8% did not adhere to antiplatelet medication or had recently stopped taking them. 81,8% did not consistently receive statin treatment as prescribed. There is a significant difference in clinical recovery levels based on the mRS among patients with and without hypertension (p=0,023); with and without hyperlipidemia (p=0,044); among patients receiving regular and irregular antithrombotic therapy (p < 0,005); among patients receiving regular and irregular statin therapy (p = 0,01).

Conclusion: Our research indicates that recurrent ischemic stroke

resulting from middle cerebral artery damage presents a higher number of risk factors, and the efficacy of recurrence prevention treatment is suboptimal.

Keywords*:* ischemic stroke, recurrence, middle cerebral artery, risk factors, recurrence prevention.

I. INTRODUCTION

Recurrent ischemic stroke is a condition that occurs in patients who have previously experienced a cerebral infarction. Despite ongoing updates in strategies for preventing recurrence, studies indicate that the recurrence rate remains relatively high, ranging from 7%-20% within 1 year to 16%-35% within 5 years...[1,2] When a recurrent stroke occurs, the prognosis is significantly worse than that of the initial stroke due to the combination of lingering effects from the previous stroke (such as motor paralysis, speech disorders, dementia) and new clinical manifestations.

Among the arterial regions, recurrent ischemic stroke in the area dominated by the middle cerebral artery accounts for the highest rate. The disease also leads to impaired neurological function, resulting in disability and increased limb issues. Treatment costs are significantly higher compared to other arterial groups.[3,4] In Vietnam, most studies focus on investigating recurrent ischemic stroke in all blood-supplying arterial areas, with limited research on recurrent ischemic stroke specifically caused by damage to the middle cerebral artery. Thus, the main objective of this study was: Discussing some risk factors for recurrent ischemic stroke caused by middle cerebral artery damage.

II. RESEARCH SUBJECTS AND METHODS

2.1. Study population

The study involved 77 patients diagnosed with recurrent ischemic stroke caused by middle cerebral artery damage. They received inpatient treatment at the Neurology Center - Bach Mai Hospital from July 2021 to August 2022.

2.1.1. Patient inclusion criteria

Patients aged 18 years and older were included if they met the clinical and brain imaging criteria. The clinical criteria consist of clinical criteria for ischemic stroke and recurrence criteria: Meeting the updated definition of central nervous system infarction as per the 2013 American Heart Association/American Stroke Association expert consensus; Simultaneously meeting the criteria for recurrent ischemic stroke: Clinical evidence of sudden onset of new focal neurological symptoms occurring 24 hours after the previous diagnosis of ischemic stroke (Patients with a confirmed diagnosis of ischemic stroke based on old hospital discharge papers, referral papers, or magnetic resonance imaging), and exclusions severe cases of the disease due to cerebral edema, mass effect, or bleeding in the infarct.

On the other hand, brain imaging criteria include: Brain magnetic resonance imaging reveals images of both new and old cerebral infarction.

2.1.2. Patient exclusion criteria

We excluded cases related to brain tumors, traumatic brain injury, or concurrent encephalitis; and patients declined to participate in the study.

2.2. Research methods

2.2.1. Study design

Cross – sectional descriptive study.

2.2.2. Data collection

Collect data according to a unified medical record form by interviewing, observing, taking history, medical history, clinical examination, testing, and research medical records. Clinically risk factors commonly found in the literature,

were collected before and during hospitalization. The risk factors included patient demographic characteristics (age, sex), medical history (hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, atrial fibrillation, history of stroke and TIA, hypercoagulable states, systemic disease), lifestyle factors (smoking and drinking), status of preventive treatment and outcome at discharge hospital based on modified Rankin scale (mRS).

2.2.3. Statistical analysis

The qualitative variables were expressed as absolute frequencies and percentages. The continuous variables were described with mean standard deviation. A Chi-square test and an independent T test were performed for the univariate analysis of the qualitative and quantitative characteristics, respectively. The P - value < 0.05 was considered to be statistically significant. The odds ratio (OR) and 95% confidence interval (95% C.I.) were calculated. All data analyses were performed using SPSS 20.0 software

III. RESULTS

In the patient study group, 71,4% were men and 28,6% were women. Out of 77 patients, the youngest was 26 years old, and the oldest was 87 years old. The average age of the group is 65 ± 11 years. The most frequent age range is 61 - 70 years old (44,2%).

3.1. Time from latest ischemic stroke to recurrence of ischemic stroke

Table 1. Time from latest ischemic stroke to recurrence of ischemic stroke

Time	n	%
< 1 month	6	7,8
1 month - < 3 months	13	16,9

Time	n	%
3 months - < 12 months	22	28,6
From 12 months and more	36	46,7
Total	77	100,0

Comment: Recurrent ischemic stroke occurs from 12 months and more after the most recent ischemic stroke, accounting for the highest rate (33,8%). The recurrence rate in the first year is 45,5%. Recurrence occurring in less than 1 month accounts for the lowest rate (7,8%). According to Nguyen Van Chuong and Nguyen Thi Thu Huyen, the highest rate of recurrent ischemic stroke after the initial ischemia is between 1 year and 5 years (61,5%), with a recurrence rate within 1 year at 18,5%[5]. According to Xu G, Liu X, the rate of recurrent ischemic stroke in the initial year was 11,2%.[6]

3.2. Percentage based on number of recurrences

Table 2. Percentage based on number of recurrences

Number of recurrences	n	%
1st	50	64,9
2nd	16	20,8
3rd	8	10,4
4th	2	2,6
5th	1	1,3
6th and more	0	0

Comment: Among the research group, 50 patients experienced their first recurrent stroke, making up the highest percentage (64,9%). There were 11 patients with a third or more recurrent ischemic stroke. According to Nguyen Van Chuong and Nguyen Thi Thu Huyen, the highest ratio of recurrent ischemic stroke occurred for the first time, accounting for 78,1%.[5]

3.3. Some risk factors for recurrent ischemic stroke caused by middle cerebral artery damage

Table 3. Baseline characteristics of patients in the study (risk factors and prevention treatment)

Risk factors	Recurrent ischemic stroke	
	n	%
Hypertension		
No	9	11,7
Yes	68	88,3
Regular treatment	49	63,6
Irregular treatment	19	24,7
Diabetes mellitus		
No	42	54,5
Yes	35	45,5
Regular treatment	24	31,2
Irregular treatment	11	14,3
Atrial fibrillation		
No	69	89,6
Yes	8	10,4
Regular treatment	4	5,2
Irregular treatment	2	2,6
Just found out during recurrent time	2	2,6
Mitral valve stenosis		
No	75	97,4
Yes	1	1,3
Just found out during recurrent time	1	1,3
Hyperlipidemia		
No	39	50,6
Yes	38	49,4
Hypercoagulable states		
No	72	93,5
Yes	5	6,5
Systemic disease		
No	75	97,4
Yes	2	2,6
History of myocardial infarction		
No	71	92,21
Yes	6	7,79

Risk factors	Recurrent ischemic stroke	
	n	%
Prior TIA		
No	62	80,5
Yes	15	19,5
Smoke		
No	45	58,4
Yes	32	41,6
Current smoker	17	22,1
Ex - smoker	15	19,5
Heavy drinking		
No	58	75,3
Yes	19	24,7
Yes and still drinking	11	14,3
Yes and have abandoned	8	10,4
Obesity		
No	59	76,6
Yes	18	23,4
Irregular physical activity	69	89,6
Unhealthy diet	70	90,9
Other risk factors	1	1,3
Treatment of hypertension		
Well - controlled(achieving a goal BP < 130/80 mmHg)	24	31,2
Not well - controlled (BP ≥ 130/80 mmHg)	44	57,1
Treatment of diabetes		
Well - controlled (achieving a goal HbA1c ≤7%)	12	15,6
Not well - controlled (HbA1c > 7%)	22	28,6
Statin therapy		
Compliant	14	18,2
Non - compliant	63	81,8
Anticoagulation therapy (In patients with atrial fibrillation)		
Compliant	4	5,2
Non - compliant	4	5,2

Risk factors	Recurrent ischemic stroke	
	n	%
Antiplatelet therapy		
Compliant	16	20,8
Non - compliant	53	68,8
Treatment of extracranial carotid stenosis		
Yes	1	1,3
No	76	98,7
Treatment of intracranial large artery atherosclerosis		
Yes	6	7,8
No	71	92,2

Comment: Most patients do not exercise regularly (89.6%) and have an unhealthy diet (90.9%). Hypertension has the highest rate among risk factors (88.3%); Hyperlipidemia follows as the second leading risk factor (49.4%); Diabetes ranks third among risk factors (45.5%).

Among the patients studied, 68.8% did not adhere to antiplatelet medication or had recently stopped taking them. 81.8% did not consistently receive statin treatment as prescribed. Out of the 8 patients with atrial fibrillation, only 4 out of 8 used anticoagulants regularly, while the others used them irregularly or had stopped. Among the 68 patients with hypertension risk factors, only 31.2% had well-controlled blood pressure. Out of the 34 patients with diabetes, 12 out of 34 (15.6%) had good blood sugar management. The percentage of patients who quit drinking and smoking was 19.5% and 10.4%, respectively. The treatment rates for carotid artery stenosis and intracranial artery stenosis were relatively low at 1.3% and 7.8%, respectively.

Relationship between certain risk factors and pre-hospital prevention treatment status with modified Rankin scale (mRS) at hospital discharge.

Table 4. Relationship between certain risk factors and pre-hospital preventive treatment status with mRS at hospital discharge.

Risk factors		mRS > 2	mRS ≤ 2	OR (95%CI)	p
		n (%)	n (%)		
Hypertension	Yes	46 (59,7%)	22 (28,6%)	7,318 (1,403 − 38,165)	0,023
	No	2 (2,6%)	7 (9,1%)		
Diabetes mellitus	Yes	24 (31,2%)	11 (14,3%)	1,636 (0,639 − 4,187)	0,351
	No	24 (31,2%)	18 (23,4%)		
Hyperlipidemia	Yes	30 (39%)	8 (10,4%)	4,375 (1,606 − 19,92)	0,044
	No	18 (23,4%)	21 (27,2%)		
Atrial fibrillation	Yes	5 (6,5%)	3 (3,9%)	1,008 (0,222 − 4,571)	1,000
	No	43 (55,8%)	26 (33,8%)		
Smoke	Yes	22 (28,6%)	10 (13,0%)	1,608 (0,620 − 4,171)	0,352
	No	26 (33,8%)	19 (24,7%)		

Risk factors		mRS > 2	mRS ≤ 2	OR (95%CI)	p
		n (%)	n (%)		
Heavy drinking	Yes	12 (15,6%)	7 (9,1%)	1,048 (0,358 – 3,602)	1,000
	No	36 (46,8%)	22 (28,6%)		
Mitral valve stenosis	Yes	1 (1,3%)	1 (1,3%)	0,596 (0,036 – 9,905)	1,000
	No	47 (61,0%)	36,4%)		
Antithrombotic Therapy	Non -compliant	43 (55,8%)	14 (18,2%)	9,214 (2,837 – 29,932)	0,000
	Compliant	5 (6,5%)	15 (19,5%)		
Statin therapy	Non -compliant	45 (58,4%)	18 (23,4%)	9,167 (2,286 – 36,755)	0,001
	Compliant	3 (3,9%)	11 (14,3%)		
Blood pressure control	Not well controlled	25 (32,5%)	19 (24,7%)	0,572 (0,221 – 1,483)	0,342
	Well controlled	23 (29,9%)	10 (13,0%)		
Diabetes control	Not well controlled	15 (19,5%)	1 (1,3%)	*	0,457
	Well controlled	8 (10,4%)	4 (5,2%)		

(: cannot be calculated)*

Comment: There is a significant difference in clinical recovery levels based on the mRS among patients with and without hypertension (p=0.023); patients with hypertension are 7.318 times more likely to experience poor recovery upon hospital discharge (mRS > 2 points) compared to patients without hypertension. Additionally, there is a significant difference in clinical recovery levels based on the mRS among patients with and without hyperlipidemia (p=0.044); patients with hyperlipidemia are 4.375 times more likely to have poor recovery upon hospital discharge (mRS > 2 points) than patients without dyslipidemia. Furthermore, there is a significant difference in clinical recovery levels based on the mRS among patients receiving regular and irregular antithrombotic therapy (p < 0.005); patients who irregularly use antiplatelet drugs or anticoagulants (for patients with atrial fibrillation) have a 9.214 times higher risk of poor recovery (mRS > 2 points) compared to patients with regular treatment. Lastly, there is a significant difference in clinical recovery levels based on the mRS among patients receiving regular and irregular statin therapy (p = 0.01); Patients receiving irregular statin therapy are 9.167 times more likely to experience poor recovery (mRS > 2 points) than patients receiving regular therapy.

Table 5. The relationship between the combination of hypertension, hyperlipidemia and diabetes with mRS at hospital discharge

Risk factors	mRS > 2		mRS≤2		OR (95%CI)	p
	n	%	n	%		
Hypertension with Hyperlipidemia	29	42,6	7	10,3	3,655 (1,243 – 10,749)	0,021
Hypertension without Hyperlipidemia	17	25,0	15	22,1		
Hypertension with Diabetes	23	33,8	9	13,2	1,444 (0,517 – 4,037)	0,605
Hypertension without Diabetes	23	33,8	13	19,2		

Comment: There is a significant difference in clinical recovery levels based on the mRS between patients with hypertension combined with hyperlipidemia and those with hypertension alone (p=0.021). Patients with risk factors for hypertension and dyslipidemia are 3.655 times more likely to experience poor recovery upon hospital discharge (mRS > 2 points) compared to patients with hypertension only.

IV. DISCUSSION

In our research, hypertension is the most common risk factor, with 68 patients accounting for 88,3%, of whom 63,6% are taking regular blood pressure medication. Within this group of 68 patients, only 31,2% have good blood pressure control. Patients with hypertension are 7,318 times more likely to have poor recovery (mRS > 2 points) than those without hypertension (p=0,023; 95%CI: (1,403 – 38,165). Patients with hypertension combined with hyperlipidemia are 3.655 times more likely to have poor recovery (mRS > 2 points) compared to patients with hypertension alone (95%CI: (1,243 – 10,749); p = 0,021). However, in our study, there was no statistically significant difference in clinical outcomes at hospital discharge based on the mRS between the group of patients with well-controlled and not well-controlled blood pressure (p = 0,342). According to Nguyen Van Chuong and Nguyen Thi Thu Huyen, 53,10% of patients are treated and regularly monitored for blood pressure, while the remaining 27% of hypertensive patients only take medication when high blood pressure is detected, experiencing unpleasant symptoms like headaches.[5] According to Nguyen Van Long, the probability of recurrent ischemic stroke in the hypertensive group is 2,7 times higher than the non-hypertensive group (95%CI: 1,55 - 4,72); in the multivariable regression analysis, hypertension was identified as an independent risk factor for recurrent ischemic stroke (OR = 2,23; 95%CI: 1,08 - 5,73).[7] Khanevski et al (2019) demonstrated that hypertension was independently linked to recurrence (HR = 1,65; 95%CI: 1,21-2,25).[8]

Hyperlipidemia is the second leading risk factor (accounting for 49,4%). Patients with hyperlipidemia were 4,375 times more likely to have poor recovery (mRS > 2 points) than patients without hyperlipidemia (95%CI: (1,606 – 19,92); p=0,044). Regarding statin therapy, 81.8% of patients did not adhere to the prescribed regimen. A significant difference in clinical outcomes at hospital discharge was observed between patients who adhered to statin therapy

and those who did not (p = 0,01). Patients with irregular statin therapy were 9,167 times more likely to experience poor clinical outcomes at discharge (mRS > 2 points) compared to those on regular therapy.[9] The SPARCL study (Stroke Prevention by Active Reduction of Cholesterol Levels), demonstrated that patients who achieved a reduction of over 50% in LDL compared to their baseline levels experienced a decrease in stroke risk by up to 31%. According to the ASA/AHA 2021 recommendations, individuals with a history of cerebral infarction or TIA and atherosclerotic disease should undergo lipid-lowering therapy targeting LDL-C levels below 70 mg/dl to lower the risk of recurrence.[10]

Diabetes is a risk factor in 45,5% of patients, with 31,2% being compliant with treatment. However, only 15,6% of diabetic patients achieved optimal glucose control (HbA1c< 7%). There was no statistically significant difference in clinical outcomes at hospital discharge based on the mRS between patients with and without diabetes (p=0,351). Similarly, we did not observe any statistically significant difference in the level of clinical outcomes at hospital discharge based on the mRS in the group of patients with hypertension combined with diabetes and hypertension not combined with diabetes (p=0,605). The role of diabetes in the risk of recurrent ischemic stroke has many conflicting opinions. Research by Nguyen Van Long, the likelihood of a second ischemic stroke recurrence in the diabetic group is 2,7 times higher than the group without diabetes (95%CI: 1,11 - 3,30), diabetes is a independent risk factor cause recurrent ischemic stroke in multivariate regression analysis.[7] According to Nguyen Thi Thu Huyen, the combination of diabetes and hypertension causes recurrent ischemic stroke to be 1,4 times higher than the first time.[5]

Of the 77 patients studied, 8 patients had atrial fibrillation (10,4%), with 2 patients having atrial fibrillation detected during the recurrent ischemic stroke for the first time, 1 patient having mitral valve stenosis (1,3%) and 6 patients had a history of myocardial infarction (7,79%). Only 4 patients consistently followed anticoagulant therapy. There was no statistically significant difference in the level of clinical recovery at hospital discharge based on the mRS in patients with and without atrial fibrillation (p=1,000), with and without mitral stenosis (p=1,000). Research by Nguyen Van Long indicates that the probability of recurrent ischemic stroke in patients with atrial fibrillation is 2,57 times greater than in patients without atrial fibrillation (95%CI: 1,14 - 5,82).[7] According to Penado et al (2003), the risk of recurrence is high for the atrial fibrillation group not using anticoagulants (HR = 2,1; 95%CI: 1,4 - 2,9, p < 0,001); Atrial fibrillation has an independent risk of recurrence in all age groups.[11]

In our research, the non-adherence rate to antiplatelet therapy was 68,8%. Patients using antiplatelet medications or anticoagulants (for those with atrial fibrillation) had a significantly higher risk of poor recovery (mRS > 2 points) at 9,214 times compared to patients receiving regular treatment (p < 0,005). Research by Nguyen Thi Thu Huyen and Nguyen Van Chuong shows that up to 73% of patients do not comply with antiplatelet drug treatment.[5] Research by Nguyen Thi Thu Huyen and Nguyen Van Chuong indicates that as many as 73% of patients fail to adhere to antiplatelet drug therapy. Additionally, research conducted by Nguyen Van Long reveals that 58,2% of patients do not adhere to antiplatelet aggregation treatment.[7] Research by Dinh Huu Hung, only 40% of patients use antiplatelet drugs regularly.[9] Research conducted

by Khanevski et al. (2019) revealed that among patients with recurrent ischemic stroke, a significant 28,8% did not utilize antiplatelet medication.[8]

The proportion of patients who were heavy drinkers in our study was 24,7%; the rate of patients quitting drinking was 19,5%. Both Vietnamese and foreign studies indicate that the relevance between alcohol and the risk of recurrence remains unclear. A study by Nguyen Van Long et al. shows that alcoholism affects the rate of recurrent ischemic stroke, but the impact is not statistically significant.[7] Study by Dinh Huu Hung shows that alcohol does not affect the risk of recurrence.[9] According to Xu et al., there is no statistically significant difference in alcohol consumption between the recurrent stroke group and the first-time stroke group.[6] Our study results showed that 41,6% of patients smoked cigarettes (including patients who had smoked and were still smoking). The rate of patients quitting smoking after previous ischemic stroke was 10,4%. According to domestic studies, the role of smoking is still unclear. Dinh Huu Hung's research and Nguyen Van Long's research have not found a relationship between tobacco addiction and the risk of recurrence.[7,9] The study by Mohan et al showed that smoking factors were not significant in predicting early recurrence.[1] Research by Chen J et al (2019) shows evidence that the risk of recurrent ischemic increases 2 times in continuous smokers compared to non-smokers.[12]

The percentage of patients with extracranial carotid artery stenosis ≥ 70% in the group of patients with mRS > 2 at discharge was 32,5%, while in the group of patients with mRS ≤ 2 at discharge, it was 10,4%. This difference is not statistically significant. According to Dinh Huu Hung and Vu Anh Nhi, carotid artery stenosis ≥

70% is an independent risk factor for an increase in recurrent ischemic stroke.[9] Research by Nguyen Van Long shows that the likelihood of recurrent myocardial infarction in the group with stenosis ≥ 70% is 3,35 times higher than in the group without stenosis or stenosis <70% (95%CI: 1,09 - 10,26).[7] Two trials NASCET and ECTS have shown a clear benefit of carotid artery surgery compared with medical therapy in patients with high-grade ICA stenosis.[10]

In the study group of patients, there were 6 patients treated for intracranial artery stenosis with dual antiplatelet therapy and statin therapy. ASA/AHA 2021 recommendations, in patients who have had a ischemic stroke or TIA with severe intracranial stenosis (70 - 99%) of a large artery, combine clopidogrel 75 mg/day with aspirin for 90 days can reduce the risk of recurrence.[10]

V. CONCLUSION

Studying 77 patients with recurrent cerebral infarction caused by damage to the middle cerebral artery, we found: Common risk factors include hypertension (88,3%), blood disorders (49,4%), and diabetes (45,5%). Other contributing factors are an unhealthy diet, lack of regular exercise, and smoking. The treatment of risk factors and prevention of recurrent cerebral infarction remains ineffective: Poorly controlled hypertension (57,1%) and diabetes (28,6%); Lack of regular treatment including antiplatelet therapy (68,8%), anticoagulant therapy (5,2%), and statin therapy (81,8%).

REFERENCES

1. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and

Cumulative Risk of Stroke Recurrence. *Stroke*. 2011;42(5):1489-1494.

2. Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2018;7(2).

3. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. *Cerebrovasc Dis*. 2003;16 Suppl 1:14-19.

4. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study. *Neurology*. 1997;48(4):891-895.

5. Nguyen Thi Thu Huyen, Nguyen Van Chuong. Research on Clinical Characteristics, Neuroimaging and Some Risk Factors in Patients with Recurrent Ischemic Stroke. Doctoral thesis in medicine. 2012.

6. Xu G, Liu X, Wu W, Zhang R, Yin Q. Recurrence after ischemic stroke in chinese patients: impact of uncontrolled modifiable risk factors. *Cerebrovasc Dis*. 2007;23(2-3):117-120.

7. Nguyen Van Long. Research on Clinical Characteristics and Some Risks in Patients with Early Recurrent Cerebral Infarction. Specialized thesis level II. 2019.

8. Khanevski AN, Bjerkreim AT, Novotny V, et al. Recurrent ischemic stroke: Incidence, predictors, and impact on mortality. *Acta Neurol Scand*. 2019;140(1):3-8.

9. Dinh Huu Hung. Risk of Recurrence After Acute Ischemic Stroke According to Stratification of Some Related Factors. Doctoral thesis in Medicine. 2014.

10. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467. doi:10.1161/STR.000000000000000375

11. Penado S, Cano M, Acha O, Hernández JL, Riancho JA. Atrial fibrillation as a risk factor for stroke recurrence. *Am J Med*. 2003;114(3):206-210. doi:10.1016/s0002-9343(02)01479-1

12. Chen J, Li S, Zheng K, et al. Impact of Smoking Status on Stroke Recurrence. *J Am Heart Assoc*. 2019;8(8):e011696. doi:10.1161/JAHA.118.011696