Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Study on Effective Factors of Secondary Prevention in Ischemic Stroke Recurrence

Vida Mamdouhi
Tabriz University of Medical Sciences
Hadi Sahrai
Tabriz University of Medical Sciences
Mazyar Hashemilar
Tabriz University of Medical Sciences
Roya Rostami
Tabriz University of Medical Sciences
Robab Mehdizadeh Esfanjani
Tabriz University of Medical Sciences
Mehdi Farhoudi
farhoudim74@gmail.com
Tabriz University of Medical Sciences

Research Article

Keywords: Ischemic stroke, recurrent stroke, medication adherence, hypertension, rehabilitation

Posted Date: November 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11497294/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background and Aim:

Recurrent ischemic stroke is a major contributor to long-term disability and healthcare burden. Identifying clinical and modifiable factors associated with recurrence is essential for improving secondary prevention. This study aimed to investigate factors associated with recurrent ischemic stroke, with particular emphasis on vascular risk factors, stroke severity, rehabilitation, lifestyle modification, and adherence to preventive pharmacotherapy.

Methods

In this retrospective case-control study, 194 patients admitted with ischemic stroke to Imam Reza Training Hospital, Tabriz, Iran, between 2016 and 2023 were evaluated. The study included 97 patients with recurrent ischemic stroke. Demographic characteristics, vascular risk factors, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), rehabilitation utilization, lifestyle factors, and use of secondary prevention medications were assessed. Between-group and within-patient comparisons were performed using appropriate parametric and non-parametric statistical tests.

Results

A history of hypertension was more common among patients with recurrent stroke than controls (83.5% vs. 60.8%, $p < 0.001$). Patients who subsequently experienced recurrent stroke had lower NIHSS scores at initial admission (median 8 vs. 10, $p = 0.057$) and at discharge (median 5 vs. 9, $p = 0.003$) than controls. Among patients with recurrent stroke, stroke severity increased at the time of recurrence, with median NIHSS increasing from 8 to 10 ($p = 0.019$). During the interval between the first and recurrent stroke, use of anticoagulants decreased from 28.6% to 17.5% ($p < 0.001$), lipid-lowering therapy from 70.1% to 49.5% ($p = 0.001$), and antiplatelet therapy from 72.2% to 48.4% ($p < 0.001$). At recurrence, fasting blood glucose increased from 109 to 117 mg/dL ($p < 0.001$), while HDL cholesterol decreased from 36 to 33 mg/dL ($p = 0.002$).

Conclusion

Recurrent ischemic stroke was associated with hypertension, a history of previous cerebrovascular events, reduced use of secondary prevention medications, lower utilization of inpatient rehabilitation, and adverse metabolic changes. Although patients who subsequently experienced recurrence initially had less severe strokes than controls, neurological severity increased at the recurrent event. These findings highlight the importance of sustained pharmacological treatment, vascular risk-factor control, and rehabilitation as components of secondary stroke prevention. Prospective multicenter studies are

warranted to determine the extent to which improving adherence and risk-factor management can reduce recurrence.

Introduction

Stroke is defined as an acute, progressive neurological deficit of vascular origin that persists for more than 24 hours or results in death. Transient ischemic attack (TIA) is a commonly used term to describe similar episodes characterized by transient symptoms lasting less than 24 hours [1]. Stroke represents the second leading cause of mortality worldwide, accounting for approximately 6.5 million deaths annually. The risk of stroke is significantly elevated, particularly among individuals with a prior history of stroke or TIA, with approximately one-third of all strokes occurring in patients who have experienced previous cerebrovascular events [2]. Blood pressure control and reduction constitute an effective therapeutic strategy for long-term stroke prevention, and the majority of clinical guidelines recommend a target blood pressure level of less than 130/80 mmHg [3].

Furthermore, patients with TIA are at high risk for subsequent stroke, with reported incidence rates of 9.9%, 13.4%, and 17.3% at 2, 30, and 90 days, respectively. Long-term cohort have demonstrated that the risk of cerebrocardiovascular events remains elevated for at least 10 years following a stroke or TIA [4]. Secondary prevention strategies focus on reducing stroke recurrence through the management of modifiable risk factors. National stroke guidelines in the United Kingdom have identified clinical conditions such as hypertension, dyslipidemia, atrial fibrillation, diabetes mellitus, and obesity, as well as lifestyle factors including smoking, physical inactivity, poor diet, and alcohol consumption, emphasizing their control as part of secondary prevention [5].

In the absence of appropriate treatment following an ischemic stroke or TIA, the risk of recurrence has been reported to be approximately 10% within one week, 15% within one month, and 18% within three months. Long-term recurrence risk extends to 25% at five years and 40% at ten years. Therefore, rapid assessment of patients with stroke or TIA and the timely initiation of appropriate treatment play a crucial role in reducing the risk of recurrence. Evidence indicates that effective treatment can reduce the risk of recurrent ischemic stroke by more than 80% [6, 7].

Recommendations for secondary prevention may be initiated as part of the patient's treatment plan from the time of hospital admission. However, primary care plays a significant role in monitoring risk factors, encouraging patients to adopt lifestyle modifications, and reassessing preventive therapies. Stroke care services should focus on improving patient adherence to pharmacological treatments and lifestyle changes [8]. Several classes of medications contribute to reducing stroke risk. For instance, long-term antiplatelet therapy in patients with a history of stroke or TIA is associated with a 25% reduction in the recurrence of vascular events [9]. Additionally, antihypertensive agents and statins exert beneficial effects on secondary prevention. Furthermore, evidences have demonstrated that moderate-to-vigorous physical activity, reduced salt intake, and dietary modification can help lower the risk of stroke and cardiovascular disease [10]. Given the importance of secondary prevention in mitigating the risk of

recurrent ischemic stroke, the present study aims to investigate the factors influencing this domain. The objective of this study is to investigate the factors influencing secondary prevention in the recurrence of ischemic stroke.

Methods

Study Population and Sample

This retrospective study included all patients presenting to Imam Reza Hospital between 2016 and 2023 who had been admitted with a diagnosis of stroke in Imam Reza Medical Center, and experienced a recurrent stroke or subsequent cerebrovascular event. These patients were identified through the stroke registry program of Neuroscience Research Center.

Sample Size

Sampling was conducted using convenience sampling from eligible patients registered in the stroke registry. The sample size was determined using a case–control ratio of 1:1. Based on the available eligible population and statistical considerations, a total of 194 participants were included, comprising 97 cases and 97 controls.

Inclusion and Exclusion Criteria

Patients meeting the following three criteria were included in the study:

1. A diagnosis of ischemic or transient stroke for which no alternative, more accurate diagnosis was established.

Informed consent

2. from the patient or their legal guardians to participate in the study and for the use of their medical information.

1. Hospitalization due to recurrent ischemic stroke or TIA.

The exclusion criteria were as follows:

1. Unwillingness of the patient or their guardians to participate in the study.
2. Establishment of a diagnosis other than stroke for the patient.
3. Presence of hemorrhagic stroke in the patient.

Control group patients were selected from among individuals who had been admitted to Imam Reza Hospital with a first-ever diagnosis of stroke. The aforementioned exclusion criteria were also applied to

the control group. A history of prior hospitalization for stroke or TIA served as an additional exclusion criterion for the control group.

3–5. Data Collection Instruments and Methods

The data collected in this study included demographic information as well as quantitative and qualitative data related to the enrolled patients. Demographic data, including age, sex, location of the brain lesion, medication history, daily activity level, adherence to medication regimens, and smoking and other substance use habits, were recorded following the collection of medical histories and patient examinations.

In this context, blood pressure control, blood glucose levels, serum lipid profiles, and body weight were assessed at the time of readmission. Furthermore, patient adherence to anticoagulant and antiplatelet medications, as well as engagement with rehabilitation interventions during the post-stroke period, was evaluated. Additionally, lifestyle modifications, including the reduction or cessation of smoking and alcohol consumption, as well as adherence to a healthy diet, were analyzed at the time of readmission. We The variables, which are collected in this study are age, antihypertensive medication, antidiabetic medication, LDL lowering, bod mass index (BMI), gender, patient activity level, Adherence to secondary preventive medications, smoking history, alcohol consumption, Use of other drugs.

Other variables

We examined The National Institutes of Health Stroke Scale (NIHSS) for severity of the stroke cases. NIHSS is a validated 15-item standardized neurological examination used to quantify the severity of acute stroke deficits, with total scores ranging from 0 (no deficit) to 42 (maximum severity) [11]. Also, modified Rankin Scale (MRS) was considered to assess functional status of the participants. MRS is a validated ordinal scale used to assess global functional disability after stroke, ranging from 0 (no symptoms) to 6 (death) [12]. In addition, Patients were considered to have received rehabilitation if their medical records documented at least one formal rehabilitation session conducted by rehabilitation specialists during hospitalization or follow-up.

Procedure and Statistical analysis

Following data collection, patients were allocated into two groups: cases and controls. The control group was randomly selected from among patients admitted for their first hospitalization at Imam Reza Hospital. Clinical data for these patients were extracted from the stroke registry system of the Neuroscience Research Center at Imam Reza Hospital. Subsequently, data pertaining to the aforementioned variables were compared between the two groups. This study specifically examined the impact of these factors on reducing the risk of stroke recurrenc within three months follow up using phone calls.

The data obtained in the present study were analyzed using SPSS statistical software version 22. Demographic variables were analyzed using descriptive statistical methods and presented as mean ± standard deviation, frequency, and percentage. Results for non-normally distributed variables were reported as median with interquartile range (IQR). The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. Independent t-tests or Mann-Whitney U tests were used to compare quantitative variables, while chi-square tests or Fisher's exact tests (depending on the reported sample sizes) were used to compare qualitative variables. Paired variables were analyzed using paired t-tests or McNemar's tests. A p-value of less than 0.05 was considered to indicate statistical significance.

Ethical Considerations

This study was conducted following the approval of the Ethics Committee of Tabriz University of Medical Sciences and Health Services, under ethics code IR.TBZMED.REC.1402.585, dated November 6, 2023. informed consent to participate was obtained from all of the participants. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and its subsequent amendments

Results

Demographic characteristics of the patients are reported in Table 1. The median age of patients was 68 years in the recurrent stroke group and 70 years in the control group. No statistically significant difference was observed between the two groups regarding age (p = 0.071). Among patients with recurrent stroke, 59 (60.8%) were female and 38 (39.2%) were male. In the control group (without recurrent stroke), 56.7% were male and 43.3% were female. No statistically significant difference was observed between the two groups regarding sex (p = 0.662). The median BMI of patients was 26.02 kg/m² in the recurrent stroke group and 25.77 kg/m² in the control group. No statistically significant difference was observed between the two groups with respect to BMI (p = 0.596).

Table 1
Demographic information of participants. *Data presented as median (interquartile range, IQR); analyzed using Mann-Whitney U test. **Data presented as frequency (percentage); analyzed using chi-square test

Variable	**Groups**		**P-value**
	Recurrent Stroke (n = 97)	**Control (n = 97)**	
Age*	68 (56.5–75)	70 (59–80.5)	0.071
Gender**			0.662
	Female	38 (39.2%)	42 (43.3%)
	Male	59 (60.8%)	55 (56.7%)
Body Mass Index (BMI)*	26.02 (23.14–29.06)	25.77 (22.95–27.50)	0.596

Comparison of Vascular Risk Factors at Initial Admission Between the Two Groups

Statistical data regarding vascular risk factors in the studied patients are reported in Table 2. In comparing vascular risk factors at initial admission between patients who subsequently experienced a recurrent stroke and those in the control group, no statistically significant differences were observed for any of the examined factors ($p > 0.05$). Regarding the comparison of snoring during sleep between the two groups, 25.8% of patients in the recurrent stroke group and 27.8% of patients in the control group reported snoring during sleep; no statistically significant difference was observed between the two groups in terms of snoring frequency ($p = 0.746$). Other factors are shown in Table 2.

Table 2
Comparison of Vascular Risk Factors at Initial Admission Between Recurrent Stroke and Control Groups. *Data presented as mean ± standard deviation; analyzed using independent t-test.

Variable	Groups		P-value
	Recurrent Stroke (n = 97)	Control (n = 97)	
Hemoglobin (Hb)*	14.11 ± 2.21	13.77 ± 2.16	0.271
Hematocrit (HCT)*	42.51 ± 5.72	41.90 ± 5.34	0.442
Systolic Blood Pressure (SBP)†	125 (120–145)	130 (120–148.5)	0.319
Diastolic Blood Pressure (DBP)†	80 (80–90)	80 (80–86.5)	0.665
Fasting Blood Sugar (FBS)†	109 (95–145.5)	113 (94.5–165)	0.200
Cholesterol (Chol)†	170 (134–203.5)	160 (137–184.5)	0.434
Triglycerides (TG)†	126 (92–192)	120 (88–168)	0.233
Low-Density Lipoprotein (LDL)†	111 (93–136)	106 (88–128.5)	0.168
High-Density Lipoprotein (HDL)†	38 (30–41)	41 (36–45)	0.001
Snoring	25 (25.8%)	27 (27.8%)	0.746

Comparison of NIHSS

The results of the analysis of National Institutes of Health Stroke Scale (NIHSS) data are presented in Table 4. The median NIHSS score on the first day of hospitalization was 8 for patients who subsequently experienced a recurrent stroke and 10 for patients in the control group. The difference between the two groups was not statistically significant, although a borderline difference was observed ($p = 0.057$).

When comparing stroke severity using the standard NIHSS classification on the first day of hospitalization, the frequency of severe stroke was 21.6% in the control group compared to 6.2% in the recurrent stroke group, while the frequency of moderate stroke was 42.3% in the control group and 71.1%

in the recurrent stroke group. These differences were statistically significant, indicating that patients who later experienced a recurrent stroke had lower stroke severity at the time of initial admission compared to the control group ($p < 0.0001$).

The median NIHSS score at discharge was 5 for patients who subsequently experienced a recurrent stroke and 9 for patients in the control group, a difference that was statistically significant ($p = 0.003$).

When comparing stroke severity using the standard NIHSS classification at discharge, the frequency of severe stroke was 25.8% in the control group compared to 3.1% in the recurrent stroke group, while the frequency of moderate stroke was 28.9% in the control group and 49.5% in the recurrent stroke group. These differences were statistically significant, indicating that patients who later experienced a recurrent stroke had lower stroke severity at discharge compared to the control group ($p < 0.0001$) again (Table 3).

Table 3
Comparison of NIHSS Between Recurrent Stroke and Control Groups. *Data presented as median (interquartile range, IQR); analyzed using Mann-Whitney U test. †Data presented as frequency (percentage); analyzed using Fisher's exact test.

Variable	NIHSS taking time	Groups		P-value
		Recurrent Stroke (n = 97)	Control (n = 97)	
Mean NIHSS	at admission*	8 (6–12)	10 (6–18.5)	0.057
Stroke severity	No stroke	2 (2.1%)	3 (3.1%)	< 0.0001
	Mild	9 (9.3%)	19 (19.6%)	
	Moderate	69 (71.1%)	41 (42.3%)	
	Moderate to severe	11 (11.3%)	13 (13.4%)	
	Severe	6 (6.2%)	21 (21.6%)	
Mean NIHSS	at Discharge*	5 (3–9)	9 (3–22)	0.003
Stroke severity	No stroke	12 (12.4%)	6 (6.2%)	< 0.0001
	Mild	30 (30.9%)	32 (33.0%)	
	Moderate	48 (49.5%)	25 (25.8%)	
	Moderate to severe	4 (4.1%)	6 (6.2%)	
	Severe	3 (3.1%)	21 (21.6%)	

Subsequently, box plots comparing NIHSS scores between the two groups on the first day of hospitalization and on the day of hospital discharge are presented (Figs. 1 and 2).

Comparison of NIHSS Between First and Recurrent Stroke on Initial and Final Days of Hospitalization

The median NIHSS score on the first day of hospitalization was 8 for the first stroke, which increased significantly to 10 for the recurrent stroke (p = 0.019). When comparing stroke severity using the standard NIHSS classification on the first day of hospitalization, the combined frequency of moderate-to-severe and severe stroke was 17.5% at the time of the first stroke; however, this difference was not statistically significant (Table 4).

Table 4
Comparison of NIHSS on Day 1 and Discharge Day Between First and Recurrent Stroke. *Data presented as median (interquartile range, IQR); analyzed using Wilcoxon signed-rank test. †Data analyzed using Maxwell-Stuart test.

Variable	NIHSS taking time	Recurrent Stroke Group (n = 97)		P-value
		First Stroke	Recurrent (Second) Stroke	
Mean NIHSS	At admission*	8 (6–12)	10 (6–18)	0.019
Stroke Severity†	No stroke	2(2.1%)	3 (3.1%)	0.072
	Mild	9 (9.3%)	17 (17.5%)	
	Moderate	69 (71.1%)	43 (44.3%)	
	Moderate to severe	11 (11.3%)	17 (17.5%)	
	Severe	6 (6.2%)	7 (17.5%)	
Mean NIHSS*	At discharge	5 (3–9)	9 (3–18)	0.267
	No stroke	12 (12.4%)	11 (11.3%)	< 0.0001
	Mild	30 (30.9%)	25 (25.8%)	
	Moderate	48 (49.5%)	29 (29.9%)	
	Moderate to severe	4 (4.1%)	12 (12.4%)	
	Severe	3 (3.1%)	20 (20.6%)	

The median NIHSS score at discharge was 5 for the first stroke and 9 for the recurrent stroke; however, this difference was not statistically significant (p = 0.267). When comparing stroke severity using the standard NIHSS classification at discharge, the combined frequency of moderate-to-severe and severe stroke was 7.2% at the time of the first stroke and 32.8% at the time of the second stroke, a difference that was statistically significant. Figures 3 and 4 shows pox plot of each group at fisrt day and at discharge.

Comparison of MRS Between the Two Groups

Statistical data regarding the Modified Rankin Scale (MRS) are reported in Table 5. MRS scores were categorized into favorable (scores 0–2) and unfavorable (scores 3–6).

In comparing MRS on the last day of hospitalization, a statistically significant difference was observed between the two groups, and patients with MRS scores of 4, 5, or 6 was higher in the control group than in the recurrent stroke group ($p < 0.0001$). Additionally, when MRS scores were categorized into favorable and unfavorable categories, a statistically significant association was found between recurrent stroke and MRS at the final day of hospitalization; the frequency of patients with unfavorable MRS was higher in the control group (57.7%) compared to the recurrent stroke group (40.2%) ($p = 0.015$).

Finally, in comparing MRS at follow-up post-hospitalization, a statistically significant difference was observed between the two groups, with MRS scores of 4, 5, or 6 was higher in the control group than in the recurrent stroke group ($p = 0.004$). However, no statistically significant association was observed between recurrent stroke and three-month MRS ($p = 0.396$).

Table 5

*MRS comparison between two groups. *Data analyzed using Fisher's exact test. †Data analyzed using chi-square test.*

Variable	MRS score	Groups		P-value
		Recurrent Stroke (n = 97)	Control (n = 97)	
MRS at discharge*	0	11 (11.3%)	7 (7.2%)	< 0.0001
	1	14 (14.4%)	17 (17.5%)	
	2	33 (34.0%)	17 (17.5%)	
	3	26 (26.8%)	15 (15.5%)	
	4	10 (10.3%)	16 (16.5%)	
	5	2 (2.1%)	3 (3.1%)	
	6	1 (1.0%)	22 (22.7%)	
	Favorable (0–2)	58 (59.8%)	41 (42.3%)	0.015
	Unfavorable (3–6)	39 (40.2%)	56 (57.7%)	
MRS follow-up*	0	12 (13.3%)	13 (17.1%)	0.004
	1	12 (13.3%)	9 (11.8%)	
	2	15 (16.7%)	6 (7.9%)	
	3	31 (34.4%)	18 (23.7%)	
	4	14 (15.6%)	14 (15.6%)	
	5	3 (3.3%)	0 (0.0%)	
	6	3 (3.3%)	16 (21.1%)	
	Favorable (0–2)	39 (43.3%)	28 (36.8%)	0.396
	Unfavorable (3–6)	51 (56.7%)	48 (63.2%)	

Comparison of History of Cardiovascular Diseases Between the Two Groups

Statistical data regarding the history of cardiovascular diseases in the study population are reported in supplementary Table 1. In comparing the prior history of cardiovascular diseases between patients who subsequently experienced a recurrent stroke and those in the control group, no statistically significant differences were observed for any of the examined factors except for hypertension (HTN). A history of HTN was present in 83.5% of patients who later developed a recurrent stroke, compared to 60.8% in the control group; thus, a statistically significant association was observed between HTN and the occurrence of recurrent stroke ($p < 0.0001$).

Comparison of atrial fibrillation Between the Two Groups

When comparing the frequency of atrial fibrillation (AF) on the first day of hospitalization, during hospitalization, and on the last day of hospitalization between patients who subsequently experienced a recurrent stroke and those in the control group, no statistically significant differences were observed regarding AF frequency at any of the specified time points (supplementary table 2).

Comparison of Rehabilitation Receipt Between the Two Groups

When comparing the frequency of rehabilitation receipt prior to hospitalization, during hospitalization, and at three-month follow-up between patients with recurrent stroke and those in the control group, no statistically significant differences were observed regarding rehabilitation receipt at pre-hospitalization or at post-hospitalization follow-up time points. However, a statistically significant difference was observed during hospitalization, whereby patients in the control group received more rehabilitation (67%) compared to those who subsequently experienced a recurrent stroke (45.5%) ($p = 0.013$). Statistical data regarding rehabilitation receipt in the study population are presented in supplementary table 3.

Comparison of History of Stroke and TIA Between the Two Groups

According to the data presented in Table 4–9, 25.8% of patients with recurrent stroke had a prior history of cerebrovascular accident (CVA), whereas none of the patients in the control group had a history of CVA, indicating a statistically significant association between prior CVA history and the occurrence of recurrent stroke ($p < 0.0001$). Six patients (6.2%) in the recurrent stroke group reported a history of transient ischemic attack (TIA), while none of the patients in the control group reported such a history. This difference between the two groups was considered statistically significant ($p = 0.029$). Furthermore, no cases of intracranial hemorrhage (ICH) or suspected subarachnoid hemorrhage (SAH) were observed in either group (supplementary table 4).

Comparison of History of Smoking, Alcohol Consumption, and Substance Use Between the Two Groups

Although the rates of smoking, substance use, and alcohol consumption were somewhat higher in the recurrent stroke group compared to the control group, no statistically significant associations were observed between smoking, substance use, or alcohol consumption and recurrent stroke (supplementary Table 5).

Comparison of Mortality Rates and Causes of Death Between the Two Groups

Based on the findings reported in Table 4–11, a total of 52 deaths were recorded during hospitalization. The data indicated that the in-hospital mortality rate in the control group (22 cases, equivalent to 22.7%)

was numerically higher than that in the recurrent stroke group (12 cases, equivalent to 12.4%); however, this difference was not statistically significant.

Regarding the causes of in-hospital mortality, all deaths in the recurrent stroke group (12 cases) were attributed to systemic complications of stroke, with no deaths due to neurological complications observed in this group. In contrast, in the control group, out of a total of 22 deaths, 18.5% were due to systemic complications and 4.1% were due to neurological complications of stroke. The comparison of the distribution of causes of in-hospital death between the two groups also did not reveal a statistically significant difference.

During the follow-up phase, the mortality rate was 8.2% in the recurrent stroke group and 10.3% in the control group, with this difference likewise failing to reach statistical significance. Regarding the causes of death at follow-up, all 8 deaths in the recurrent stroke group were attributed to systemic complications of stroke. In the control group, however, among the 10 deaths, 8 were due to systemic complications, 1 was related to neurological complications, and 1 was attributed to other causes.

Comparison of Stroke Etiology Between the Two Groups

In examining the association between stroke etiology and the occurrence of recurrent stroke, no statistically significant associations were observed for any of the evaluated etiological factors (supplementary Table 7).

Comparison of TPA Treatment and Post-Treatment Hemorrhage Between the Two Groups

The frequency of treatment with tissue plasminogen activator (TPA) was 33% in the recurrent stroke group and 21.6% in the control group. No statistically significant association was observed between TPA administration and the occurrence of recurrent stroke. Among TPA recipients, two patients in the recurrent stroke group developed intracranial hemorrhage (ICH); however, no cases of ICH following TPA administration were observed in the control group ($p = 0.497$). Mechanical thrombectomy was not performed for any patient in either the control group or the recurrent stroke group (supplementary Table 8).

Comparison of Anticoagulant Treatment Between the Two Groups

A total of 58 patients had a cardioembolic etiology for stroke, of whom 26 belonged to the recurrent stroke group and 32 to the control group. In addition, two patients (one from each group) developed deep vein thrombosis during hospitalization. These 60 patients received anticoagulant therapy. The rate of NOAC (novel oral anticoagulant) receipt was reported as 15.5% in the recurrent stroke group and 17.5% in the control group. The rate of warfarin receipt was reported as 11.3% in the recurrent stroke group and 17.5% in the control group. Although the percentage of warfarin receipt was somewhat lower

in the recurrent stroke group compared to the control group, no statistically significant difference was observed between the two study groups regarding warfarin receipt (supplementary Table 9).

Comparison of Antiplatelet Treatment Between the Two Groups

Statistical data regarding antiplatelet treatment in the study population are presented in supplementary Table 10. The frequency of antiplatelet receipt was 72.2% in the recurrent stroke group and 65.9% in the control group. The frequency of receiving clopidogrel with aspirin (ASA) was reported as 43.3% in the recurrent stroke group and 30.9% in the control group

Comparison of BMI and Laboratory Parameters Between First and Recurrent Stroke

The mean BMI at the time of the first stroke and recurrent stroke was 26.15 kg/m² and 25.51 kg/m², respectively, with no statistically significant difference observed. Furthermore, differences in systolic blood pressure, diastolic blood pressure, hematocrit, and triglyceride levels between the time of recurrent stroke and the first stroke were not statistically significant (supplementary Table 11).

The mean hemoglobin level at the time of the first stroke was 14.11 g/dL, which decreased to 13.58 g/dL at the time of recurrent stroke, a difference that was statistically significant ($p = 0.002$). The median fasting blood glucose level at the time of the first stroke was 109 mg/dL, which demonstrated a substantial increase to 117 mg/dL at the time of recurrent stroke ($p < 0.0001$). It may show that elevated blood glucose levels play a significant role in the occurrence of recurrent stroke (Fig. 3).

The median cholesterol level in the first stroke was 170 mg/dL, which increased to 215 mg/dL in the recurrent stroke. Similarly, the median LDL level rose from 102 mg/dL in the first stroke to 140 mg/dL in the recurrent stroke. However, the increases in total cholesterol and LDL levels in the recurrent stroke compared to the prior stroke were not statistically significant. Furthermore, the median HDL level in the first stroke was 36 mg/dL, which decreased to 33 mg/dL in the recurrent stroke, and this difference was statistically significant. It can be concluded that a reduction in HDL levels may play a role in the occurrence of recurrent stroke (p-value = 0.002).

Association of Reduction in Smoking, Substance Use, and Alcohol Consumption with Recurrent Stroke

The frequency of smoking decreased from 17.5% at the time of the first stroke to 15.5% at the time of recurrent stroke. The frequency of substance uses also decreased from 6.2% to 4.1%. Furthermore, the frequency of alcohol consumption decreased from 4.1% at the time of the first stroke to 1.0% at the time of recurrent stroke. However, no statistically significant associations were observed between these factors and the occurrence of recurrent stroke (supplementary Table 12).

Comparison of Rehabilitation Receipt Between the Two Groups

In comparing the frequency of rehabilitation receipt before hospitalization, during hospitalization, and at the three-month follow-up, no statistically significant differences were observed between patients with recurrent stroke and those in the control group regarding rehabilitation utilization prior to admission or during the post-discharge follow-up period. However, a statistically significant difference was noted between the two groups with respect to rehabilitation receipt during hospitalization, such that patients in the control group received more rehabilitation (67%) compared to those who subsequently experienced recurrent stroke (45.5%) (p-value = 0.013). (supplementary Table 13).

Comparison of Medication History Before and During Hospitalization Between Two Groups

Statistical data regarding the patients' medication history are reported. In comparing the administration of antidiabetic, antihyperlipidemic, and anticoagulant, before and during hospitalization between patients who subsequently experienced recurrent stroke and those in the control group, no statistically significant differences were observed for any drug category, with the exception of antihyperlipidemic use prior to hospitalization. Specifically, 25.8% of patients who later developed recurrent stroke had received antihyperlipidemic agents, whereas this rate was 13.4% in the control group (p-value = 0.030). (supplementary Table 14).

Association of Adherence to Pharmacological Treatment with Reduction in Recurrent Stroke

The rate of antidiabetic medication use during hospitalization for the first stroke was 24.7%; this rate changed to 22.7% prior to the second hospitalization at the time of recurrent stroke, demonstrating no statistically significant difference (supplementary Table 15). In contrast, the rate of anticoagulant use during hospitalization for the first stroke was 28.6, which decreased to 17.5% prior to the second hospitalization at the time of recurrent stroke, showing a statistically significant difference ($p < 0.001$). The rate of antihyperlipidemic medication use during hospitalization for the first stroke was 70.1%, which decreased to 49.5% prior to the second hospitalization at the time of recurrent stroke; this reduction demonstrated a statistically significant association with the occurrence of recurrent stroke ($p = 0.001$). However, no statistically significant difference was observed between the 67.0% rate of antihypertensive medication use at the first admission and the 56.7% rate at the second admission for recurrent stroke.

Association of Adherence to Antiplatelet Therapy with Reduction in Recurrent Stroke

The rate of antiplatelet consumption during hospitalization in the initial stroke was 72.2%, which decreased to 48.4% prior to the second hospitalization at the time of recurrent stroke; this reduction was evaluated as statistically significant (p-value < 0.001)

Factors for Third Stroke in Patients with Recurrent Stroke

A total of four patients (4.1%) with recurrent stroke experienced a third stroke. Among these patients, one was female and three were male. The median age of these patients was 51.5 years. Clinical indicators of risk factors for these patients are presented in (supplementary Table 16).

Discussion

This study, comparing 97 patients with recurrent stroke and 97 patients with first-ever stroke, demonstrated that patients with recurrent stroke had a higher prevalence of prior hypertension (83.5% vs. 60.8%), previous stroke (25.8% vs. 0%), and TIA (6.2% vs. 0%) compared to the control group. However, this group exhibited lower initial stroke severity (median NIHSS: 8 vs. 10) and greater improvement (median NIHSS at discharge: 5 vs. 9). Additionally, comparing MRS at follow-up, the MRS scores of 4, 5, or 6 was higher in the control group than in the recurrent stroke group ($p = 0.004$); however, differences was observed between recurrent stroke and three-month MRS ($p = 0.396$). Furthermore, elevated blood glucose levels (109 mg/dL to 117 mg/dL) and reduced HDL levels (36 mg/dL to 33 mg/dL) at the time of recurrent stroke, and rise in LDL and total cholesterol level. These findings suggest that modifiable factors, including treatment adherence and metabolic changes, may play a role in the occurrence of recurrent stroke.

Moreover, study of over 70,000 diabetic patients, which showed that diabetes pharmacotherapy using Lobeglitazone reduces the risk of stroke recurrence by up to 26% (OR 0.74; 95% CI 0.61–0.90; $p = 0.002$) [13]. Furthermore, in a study of 84 diabetic patients with ischemic stroke, those with recurrent stroke had a higher frequency of hypoglycemic therapy (36.9% vs. 23.3%) and higher mean heart rate (78.29 vs. 74.88) [14]. These results suggest that diabetes management may reduce recurrent stroke risk not only through blood glucose reduction but also by preventing glycemic fluctuations and controlling heart rate.

The findings of the present study demonstrated that a history of hypertension (HTN) is significantly associated with recurrent stroke. This finding is consistent with the results of a recent study involving 1,072 patients, which reported that patients with recurrent stroke had a higher prevalence of cardiac disease and diabetes [15]. This association was confirmed in another study focusing on a younger population (mean age 45.4 years), which identified hypertension as a key factor in recurrent stroke [16]. However, it is noteworthy that the association between HTN and recurrent stroke in the present study is strengthened in the context of reduced medication adherence, as a study of 1,041 patients demonstrated that approximately one-third of patients do not adhere to guideline-recommended secondary prevention [17]. This gap in treatment adherence is corroborated by findings from research utilizing UK Biobank data, published in 2024, which showed that stroke patients, compared to myocardial infarction (MI) patients, had lower odds ratios for blood pressure control (OR = 0.63) and antiplatelet medication use (OR = 0.30) [18]. Therefore, although hypertension represents a modifiable risk factor, inadequate adherence to essential treatments may exacerbate its impact.

Reduced use of anticoagulant and antiplatelet medications prior to recurrent stroke was observed, demonstrating a significant association with the occurrence of the second event. This finding aligns with a study of 7,315 participants, which reported that stroke patients, on average, had lower utilization of antiplatelet and anticoagulant agents compared to MI patients [18]. In contrast, dual antiplatelet therapy (DAPT) in a clinical trial of 1,920 patients demonstrated a 3.3% reduction in stroke recurrence, particularly in patients with low NIHSS scores (≤ 5) [18]. These findings underscore that the combination of high adherence to preventive medications and appropriate treatment selection can reduce the risk of recurrent stroke.

Furthermore, studies have reported that congestive heart failure (CHF) and a history of diabetes are major risk factors for recurrent stroke, increasing the likelihood of recurrence of stroke (OR: 3.45 and 1.71), respectively [19, 20]. This evidence show that although patients with recurrent stroke present with lower severity at initial hospitalization, a prior history of stroke and comorbid conditions dramatically increase the risk of subsequent events.

In the present study, reduced use of anticoagulant and antiplatelet medications prior to recurrent stroke was observed, demonstrating a significant association with the occurrence of the second event. a recent meta-analysis based on data from 6,442 patients with ischemic stroke and atrial fibrillation (AF) confirmed the safety of early initiation of anticoagulant therapy, although its effect on reducing recurrent stroke remained uncertain. This conclusion is reinforced in the present study by the reduced anticoagulant consumption in the recurrent stroke group (17.5%), indicating that even when treatments are effective, inadequate adherence can diminish their efficacy [21].

In our study a reduction in smoking frequency in recurrent stroke was observed, although this difference was not statistically significant. Nevertheless, findings from other studies indicate that even indirect exposure to cigarette smoke increases stroke risk by 25% [22]. Additionally, a study of 266 patients reported that alcohol consumption (in 45.5% of patients) and hypertension are major risk factors for recurrent stroke [23]. Therefore, in addition to pharmacological management, reducing environmental factors and implementing lifestyle modifications (such as avoiding alcohol and cigarette smoke) may contribute to reducing recurrent stroke risk.

Consistent with the findings of the present study, when comparing stroke severity using the standard NIHSS classification at discharge, the frequency of severe stroke in the control group was significantly higher than in the recurrent stroke group. Thus, patients who subsequently experienced a recurrent stroke had lower stroke severity at discharge compared to the control group. This phenomenon may potentially be attributed to patients not taking their first stroke seriously, leading to failure to undertake preventive measures and non-adherence to lifestyle modifications. According to the results of a cross-sectional study in China, over 46% of patients who experienced a first-ever stroke subsequently neglected preventive measures [24]. Although previous study by Skajaa et al. have identified recurrent stroke as a risk factor for mortality (25% and 75% for all cause mortality) [25], the explanation for this finding in the present study may be the higher frequency of moderate-to-severe strokes in the control

group (35%) compared to the case group (17.5%). Consequently, this issue warrants more detailed investigation in future studies.

Patients who reduce their adherence to pharmacological and rehabilitation therapies after a first stroke, may lead to recurrent stroke. Pattern was confirmed in a study of 100 patients with recurrent stroke, which identified alcohol consumption and sedentary lifestyle as modifiable factors in stroke recurrence [16]. However, the primary challenge is implementation; a study of 1,041 patients from southern China reported that approximately one-third of patients do not adhere to secondary prevention, even when they have multiple risk factors [17]. Proposed strategies to break this cycle include: (1) establishing active follow-up systems to assess medication adherence, (2) focusing on blood glucose management (identified as a major risk factor in this study), and (3) implementing physical activity plans adapted to patient conditions. Another study of 75 patients emphasized that even mild physical activity reduces recurrent stroke risk [26]. This shows the necessity of a multidimensional approach to secondary prevention that focuses on lifestyle improvement in addition to pharmacotherapy. A study from Tunisia involving 782 patients showed that although statin use increased from 38.9% to 70.3%, adherence to non-pharmacological modifications (such as healthy diet or smoking cessation) decreased [27]. This evidence indicates that while pharmacological approaches have advanced, educational programs and lifestyle modifications still require greater attention.

Study Limitations

Although the present study has yielded significant evidence, several limitations should be considered when interpreting its findings. The most important limitations of the current study include the limited sample size, its single-center design, restricted population diversity, the case-control design, as well as the limited follow-up duration. These limitations are expected to be addressed in future research.

Conclusion

This study demonstrated that modifiable factors, including non-adherence to pharmacological therapies, reduced rehabilitation utilization, and metabolic changes (elevated blood glucose and reduced HDL), may play a role in the occurrence of recurrent stroke. Although patients with recurrent stroke experienced lower severity during their initial event, reduced adherence to preventive measures and an increased burden of modifiable risk factors exacerbated the risk of a second event. These findings are consistent with global evidence emphasizing that inadequate adherence to secondary prevention therapies (even in the presence of effective treatments such as statins and anticoagulants) and lifestyle modifications (e.g., reduced physical activity) are key factors in stroke recurrence.

Data availability

All data supporting the findings of this study are included in the article and its Supplementary Information. Additional information is available from the corresponding author upon request.

Declarations

Data availability

All data supporting the findings of this study are included in the article and its Supplementary Information. Additional information is available from the corresponding author upon request.

Acknowledgements

During the preparation of this article, the authors used ChatGPT by OpenAI to improve paper readability.

Competing interests

The authors declare no competing interests.

Author contribution

V.M. and H.S. contributed to the conception and design of the study, data acquisition, and drafting of the manuscript. M.H. and R.R. contributed to data acquisition, analysis, and interpretation of the data. R.M.E. performed the statistical analysis and contributed to the interpretation of data. M.F. contributed to the conception and design of the study, critical revision of the manuscript for important intellectual content, and supervised the study.

All authors read and approved the final manuscript.

Funding

None

Consent to publish

Not Applicable

References

1. Kuriakose D, Xiao Z. Pathophysiology and treatment of stroke: present status and future perspectives. International journal of molecular sciences. 2020;21(20):7609
2. Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. Neurology. 2021;97(20_Supplement_2):S6-S16
3. Heran M, Lindsay P, Gubitz G, Yu A, Ganesh A, Lund R, et al. Canadian stroke best practice recommendations: acute stroke management, practice guidelines update, 2022. Canadian Journal of Neurological Sciences. 2024;51(1):1-31
4. Vinding NE, Butt JH, Lauridsen MD, Kristensen SL, Johnsen SP, Krøll J, et al. Long-term incidence of ischemic stroke after transient ischemic attack: a nationwide study from 2014 to 2020. Circulation.

2023;148(13):1000-10

5. Bhalla A, Clark L, Fisher R, James M. The new national clinical guideline for stroke: an opportunity to transform stroke care. Clinical Medicine. 2024;24(2):100025
6. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke–a systematic review and meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 2021;30(8):105935
7. Amarenco P. Atorvastatin in prevention of stroke and transient ischaemic attack. Expert Opinion on Pharmacotherapy. 2007;8(16):2789-97
8. Morris JG, Carter EL, Martin SA. Stroke: Secondary prevention of ischemic events. J Family Pract. 2017;66:420-7
9. Bhatia K, Ladd LM, Carr KH, Di Napoli M, Saver JL, McCullough LD, et al. Contemporary antiplatelet and anticoagulant therapies for secondary stroke prevention: a narrative review of current literature and guidelines. Current Neurology and Neuroscience Reports. 2023;23(5):235-62
10. Diener H-C, Hankey GJ. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar. Journal of the American College of Cardiology. 2020;75(15):1804-18
11. Alamri AF, Alamri FF, Alkhiri A, Alturki F, Alatawi Y, Alraddadi EA, et al. National Institute of Health Stroke Scale (NIHSS) Scoring Tool Utilizing Medical Records: A Single-Center Validation Study. Medical Principles and Practice. 2025
12. Nair S, Hurly J, Saylor D. Evaluating the strengths and limitations of structured modified rankin scale validation studies–A systematic review. Journal of Stroke and Cerebrovascular Diseases. 2025;34(5):108242
13. Yoo J, Jeon J, Baik M, Kim J. Lobeglitazone, a novel thiazolidinedione, for secondary prevention in patients with ischemic stroke: a nationwide nested case-control study. Cardiovasc Diabetol. 2023;22(1):106.10.1186/s12933-023-01841-4
14. Wang L, Li H, Hao J, Liu C, Wang J, Feng J, et al. Thirty-six months recurrence after acute ischemic stroke among patients with comorbid type 2 diabetes: A nested case-control study. Front Aging Neurosci. 2022;14:999568.10.3389/fnagi.2022.999568
15. Yang M, Ju KJ, Chen P, Zhong LL. Risk Factors for Recurrent Stroke and the Impact of Targeted Health Management. Risk Manag Healthc Policy. 2025;18:2759-67.10.2147/rmhp.S531041
16. Wongrostrai Y, Chiangkhong A, Suwanwong C, Khunakorncharatphong A. Lifestyle and Occupational Factors Associated with Recurrent Stroke among Working-Age Adults in Urban Areas of Thailand. F1000Res. 2024;13:1445.10.12688/f1000research.154968.3
17. Zhong X, Li L, Ye Q, Wang J, He L, Li C. Cognition and influencing factors of secondary prevention in patients with ischemic stroke 1 year after discharge in Southwest China: a cross-sectional survey. Front Neurol. 2024;15:1488180.10.3389/fneur.2024.1488180
18. Rivier CA, Acosta JN, Leasure AC, Forman R, Sharma R, de Havenon A, et al. Secondary Prevention in Patients With Stroke Versus Myocardial Infarction: Analysis of 2 National Cohorts. J Am Heart Assoc. 2024;13(9):e033322.10.1161/jaha.123.033322

19. Kamgang J, Tétinou F, Zolo Y, Tan CY, Wambo C, Fongang EJN, et al. Recurrent Ischemic and Hemorrhagic Stroke in Cameroon: A Case-Control Study. Neurol Res Int. 2021;2021:9948990.10.1155/2021/9948990
20. Guo J, Guan TJ, Wang LD, Chao BH, Liu YL. [The risk factors of first recurrence in ischemic stroke patients in different periods after first attack]. Zhonghua Yu Fang Yi Xue Za Zhi. 2021;55(9):1105-13.10.3760/cma.j.cn112150-20210719-00689
21. Pereira V, Marino M, Hornik A, Hornik J, Henson J, Wesler J, et al. Comparison of early vs late anticoagulation for secondary stroke prevention in patients with atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. J Thromb Thrombolysis. 2025;58(7):893-900.10.1007/s11239-025-03139-6
22. Okekunle AP, Asowata OJ, Fakunle AG, Akpa OM, Sarfo FS, Akpalu A, et al. Secondhand smoke exposure is independently associated with stroke among non-smoking adults in West Africa. J Neurol Sci. 2022;443:120489.10.1016/j.jns.2022.120489
23. Dabilgou AA, Dravé A, Kyelem JMA, Zoungrana R, Napon C, Millogo A, et al. Frequency of recurrent stroke in Burkina Faso: an observational hospital based study of 6 months. Pan Afr Med J. 2021;40:108.10.11604/pamj.2021.40.108.23098
24. Ren H, Guo YF, Zhang ZX, Lin BL, Mei YX, Wang WN, et al. Perception of recurrent risk versus objective measured risk of ischemic stroke in first-ever stroke patients from a rural area in China: A cross-sectional study. Patient Educ Couns. 2023;107:107586.10.1016/j.pec.2022.107586
25. Skajaa N, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, et al. Risks of Stroke Recurrence and Mortality After First and Recurrent Strokes in Denmark: A Nationwide Registry Study. Neurology. 2022;98(4):e329-e42.10.1212/wnl.0000000000013118
26. Aini N, Darojat ZW. Association Between Physical Activity and Stroke Recurrence: A Cross-Sectional Study. Florence Nightingale J Nurs. 2025;33(1):1-6.10.5152/fnjn.2025.24221
27. Ben Mansour N, Lassoued O, Saidi O, Aissi W, Ben Ali S, Ben Romdhane H. Trends in secondary prevention of coronary heart disease in Tunisia: prevention of recurrences of MI and stroke. Glob Heart. 2012;7(4):361-6.10.1016/j.gheart.2012.01.002

Figures

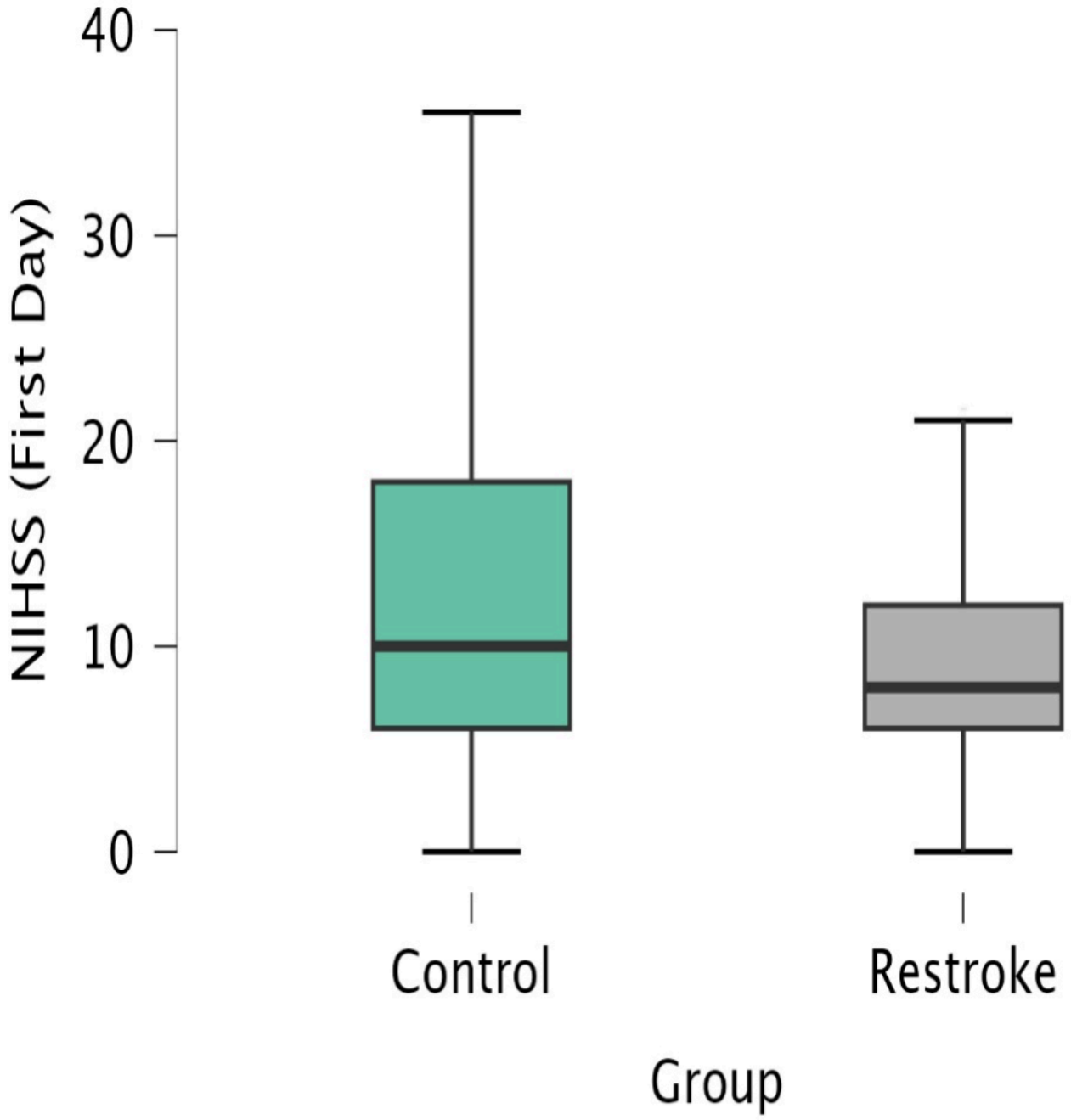


Figure 1

Boxplot NIHSS at admission comparison between two groups.

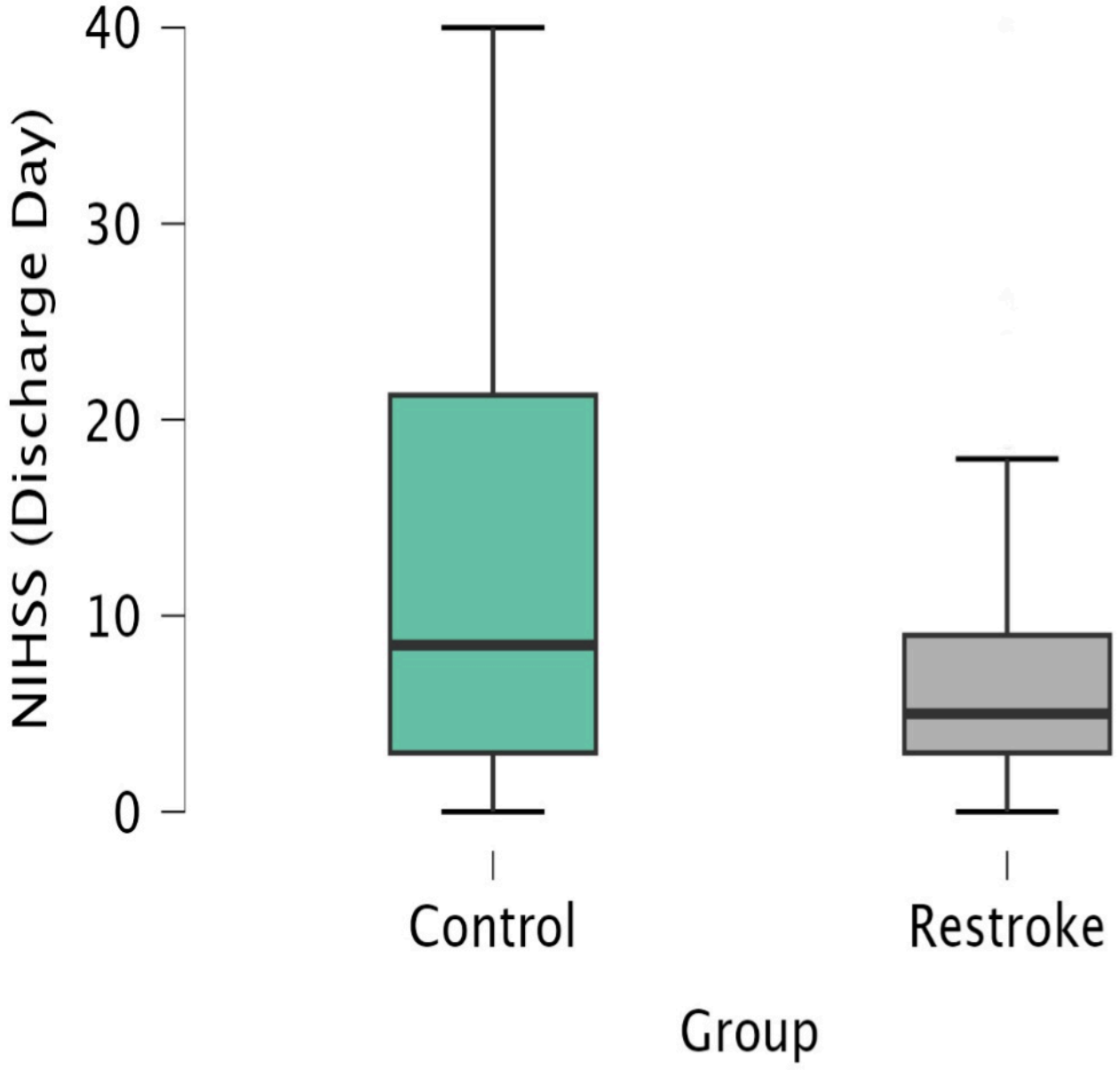


Figure 2

Boxplot for NIHSS at discharge, comparison between two group

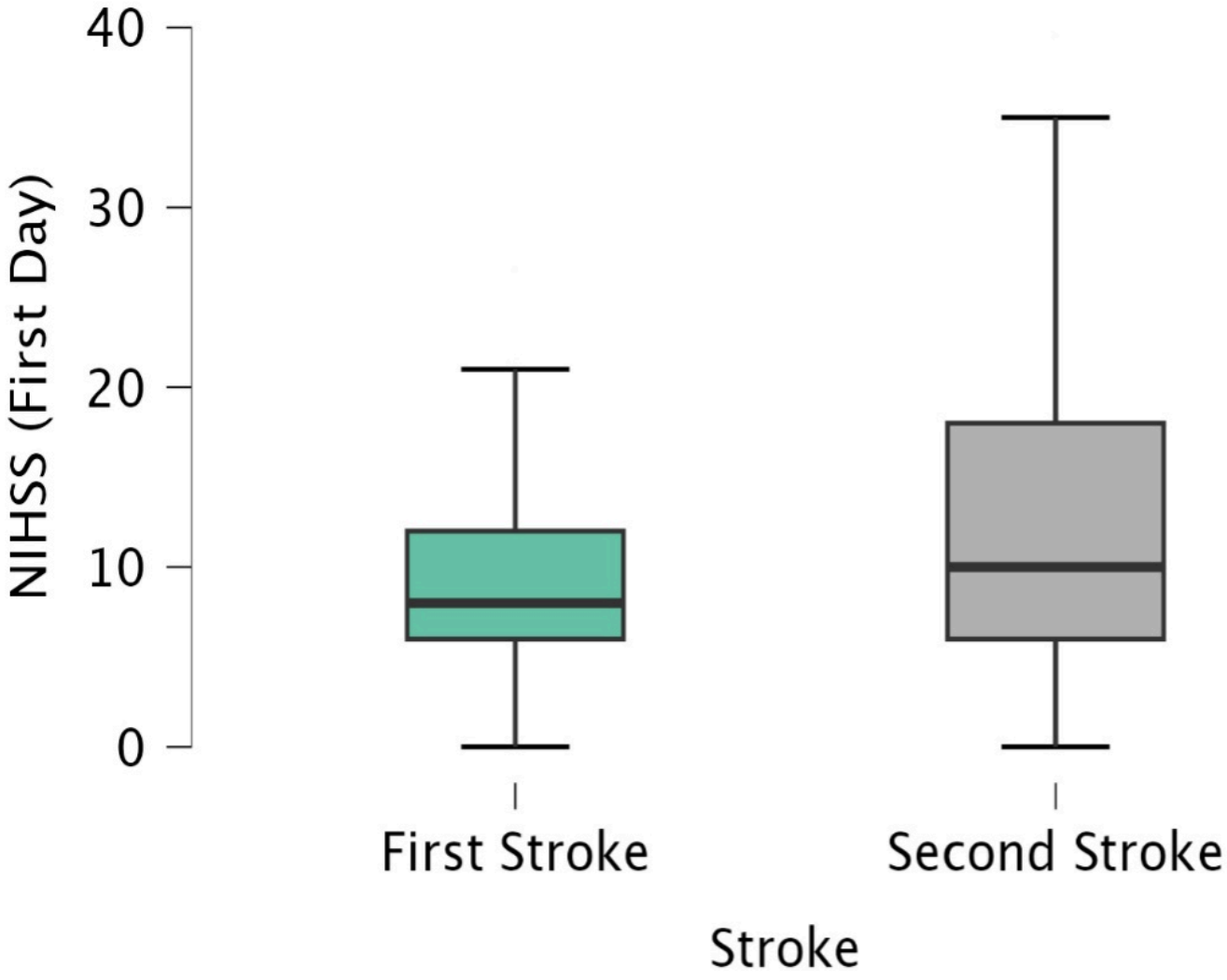


Figure 3

the Comparison of NIHSS between first stroke group and second stroke.

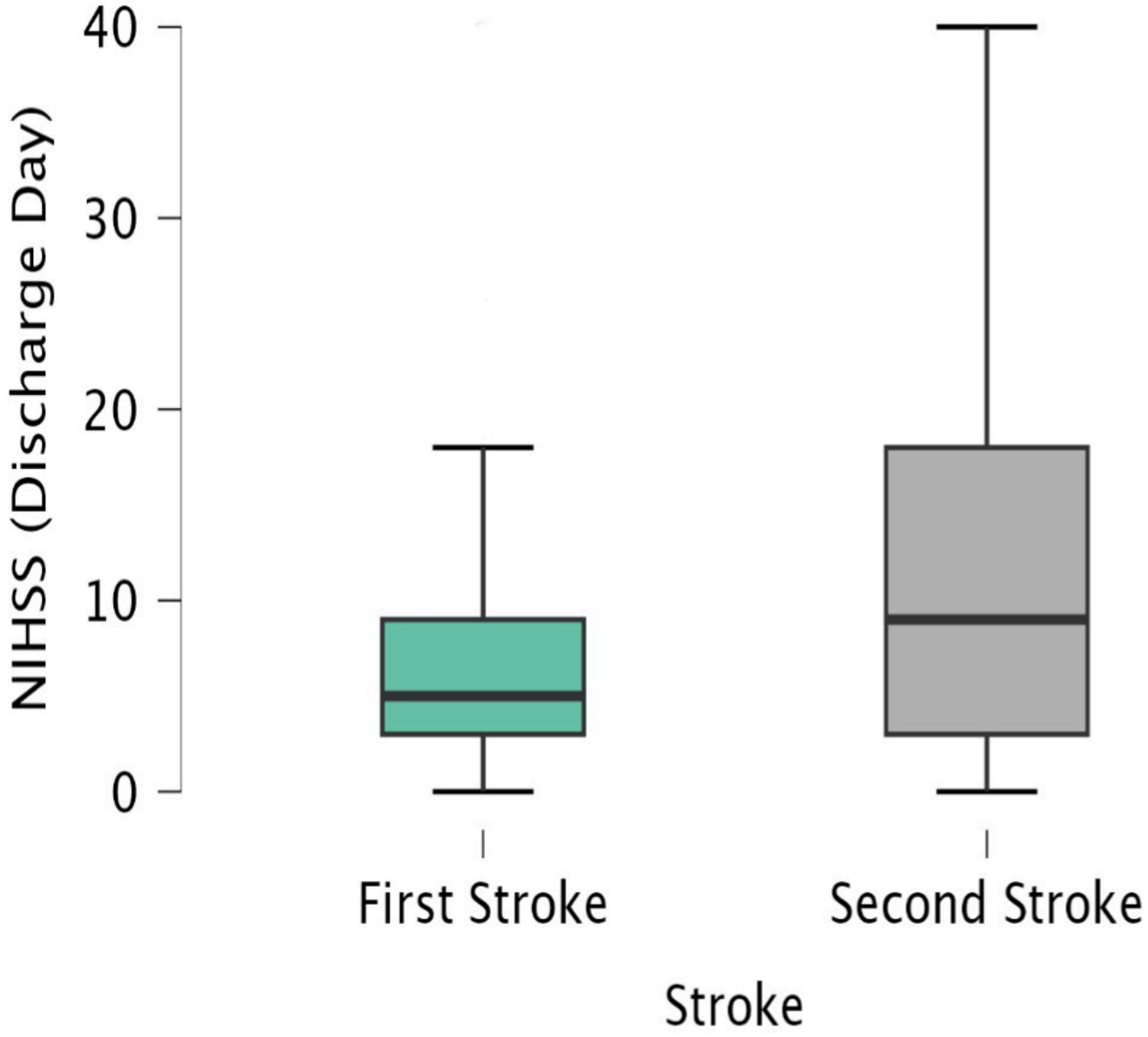


Figure 4

The comparison of NIHSS at discharge between first stroke and second stroke.

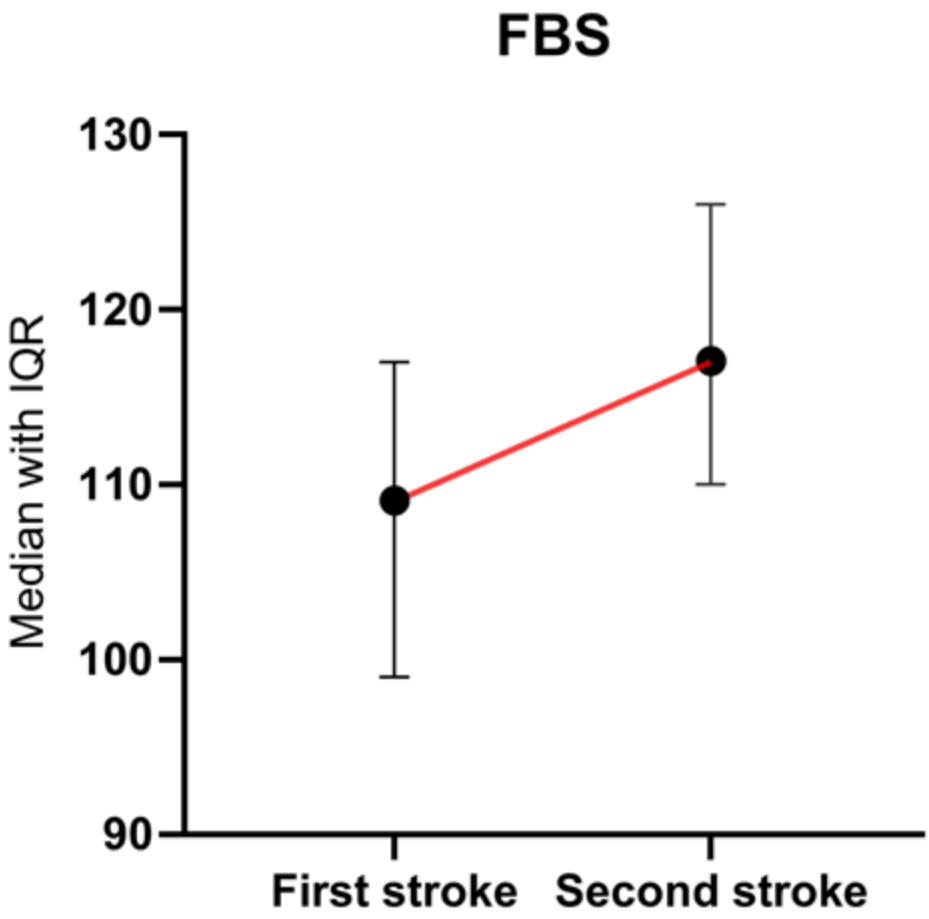


Figure 5

Comparison of FBS Changes Between First and Recurrent Stroke in Patients with Recurrent Stroke.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- tablestroke.docx