

Determinants of stroke recurrence in a nationwide multicenter cohort

Nazlı Gamze Bülbül¹, Bilge Piri Çınar², Refik Kunt³, Burcu Yüksel⁴, Halil Güllüoğlu⁵, İdris Saylır⁶, Sibel Çeliker Uslu⁷, Eylem Özyaydın Göksu⁸, Baykal Yıldız⁹, Didem Öz¹⁰, Ahmet Onur Keskin¹¹, Osman Korucu¹², Çetin Kürşad Akpınar², Volkan Solmaz¹³, Meliha Türksever¹³, Fatma Zehra Altunç⁸, Zeynep Elmas¹⁴, Mustafa Ekici¹⁵, Murat Mert Atmaca¹, Sibel Karşıdağ¹, Mehmet Fatih Özdağ¹

¹Department of Neurology, University of Health Sciences, Sultan Abdülhamid Han Training and Research Hospital, İstanbul, Türkiye

²Department of Neurology, Samsun University Faculty of Medicine, Samsun, Türkiye

³Department of Neurology, İzmir Democracy University Faculty of Medicine, İzmir, Türkiye

⁴Department of Neurology, İstanbul Bakırköy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Hospital, İstanbul, Türkiye

⁵Department of Neurology, Medicalpoint International İzmir Hospital, İzmir, Türkiye

⁶Department of Neurology, University of Health Sciences, Samsun Training and Research Hospital, Samsun, Türkiye

⁷Department of Neurology, İstanbul University Faculty of Medicine, İstanbul, Türkiye

⁸Department of Neurology, Antalya Research and Training Hospital, Antalya, Türkiye

⁹Department of Neurology, Kocaeli Darıca Farabi Research and Training Hospital, Kocaeli, Türkiye

¹⁰Department of Neurology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

¹¹Department of Neurology, Eskişehir City Hospital, Eskişehir, Türkiye

¹²Department of Neurology, Atatürk Sanatoryum Research and Training Hospital, Ankara, Türkiye

¹³Department of Neurology, Trakya University Faculty of Medicine, Edirne, Türkiye

¹⁴Department of Neurology, Medicalpark İzmir Hospital, İzmir, Türkiye

¹⁵Emergency Medicine, Atatürk State Hospital, Aydın, Türkiye

ABSTRACT

Objectives: This multicenter study aimed to identify the clinical, laboratory, and demographic determinants associated with stroke recurrence in a large nationwide cohort of patients presenting with acute stroke.

Patients and methods: This retrospective multicenter cohort study included 1,132 patients (614 males, 518 females; mean age: 70.0 ± 12.6 years) who hospitalized with acute stroke across tertiary centers in Türkiye between February 2016 and December 2024. Sociodemographic characteristics, vascular risk factors, clinical presentation, laboratory parameters, neuroimaging findings, and clinical outcomes were obtained from hospital records. Stroke recurrence was defined as the primary endpoint. Bivariate analyses were initially performed to evaluate associations between potential predictors and recurrence, followed by multivariate logistic regression analysis to determine independent determinants.

Results: Stroke recurrence occurred in 24.3% of the cohort. In bivariate analyses, recurrence was significantly associated with hypertension (odds ratio [OR] = 1.677, $p = 0.002$), hyperlipidemia (OR = 1.575, $p = 0.01$), diabetes mellitus (OR = 1.390, $p = 0.025$), atrial fibrillation (OR = 2.531, $p < 0.001$), and carotid artery stenosis (OR = 3.085, $p < 0.001$). However, in multivariate logistic regression analysis, only advanced age (OR = 1.030, $p < 0.001$) and carotid artery stenosis (OR = 3.085, $p < 0.001$) remained independent predictors of stroke recurrence.

Conclusion: Advanced age and carotid artery stenosis emerged as the strongest independent determinants of stroke recurrence in this nationwide multicenter cohort. These findings highlight the importance of early vascular evaluation and individualized risk stratification to improve secondary stroke prevention strategies.

Keywords: Acute stroke, carotid artery stenosis, risk factors, secondary prevention, stroke recurrence.

Correspondence: Nazlı Gamze Bülbül, MD. SBÜ Sultan Abdülhamid Han Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, 34668 Üsküdar, İstanbul, Türkiye.

E-mail: nzl.gmzb@gmail.com

Received: December 08, 2025 **Accepted:** April 01, 2026 **Published online:** May 25, 2026

Cite this article as: Bülbül HG, Çınar BP, Kunt R, Yüksel B, Güllüoğlu H, Saylır İ, et al. Determinants of stroke recurrence in a nationwide multicenter cohort. Turk J Neurol 2026;32(2):155-164. https://doi.org/10.55697/tnd.2026.613.

Recurrent ischemic strokes remain a major clinical concern, posing a significant threat to individual functional independence and placing an escalating burden on healthcare systems.^[1,2] In recent years, poststroke survival rates have improved in parallel with advances in acute treatment protocols and the broader application of recanalization therapies. This progress has, in turn, heightened the importance of long-term secondary prevention strategies.^[3,4] Beyond the increased risk of mortality, recurrent strokes substantially impact patients' lives through secondary effects such as cognitive decline, reduced quality of life, employment loss, and psychosocial complications.^[2]

Recurrent stroke refers to the occurrence of a new cerebrovascular event following a previous stroke, typically after a symptom-free interval. According to widely accepted definitions, a recurrent ischemic stroke is distinguished from progression of the index event by the appearance of new neurological symptoms corresponding to a different vascular territory, or by new lesions on neuroimaging that are anatomically distinct from the original infarct.^[1,5,6] The recurrence may occur in the same or a different vascular region, but it must be temporally separated from the initial episode by a clinically stable period. Previous studies have demonstrated that the recurrence rate varies depending on stroke subtype and underlying pathophysiology, being higher among patients with cardioembolic and large-artery atherosclerotic strokes.^[7,8] The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification^[9] was employed in multiple large-scale studies assessing recurrence patterns.^[10,11]

Although the risk of recurrence declines over time, it is never fully resolved. Evidence shows that recurrence risk peaks within the first year and then plateaus at a clinically significant level in the following years.^[4,12] This underscores the need for sustainable secondary prevention strategies that extend beyond the acute phase and incorporate long-term monitoring and interventions. Numerous studies have identified classic vascular risk factors, including age, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidemia, carotid artery stenosis, and the severity of previous stroke or transient ischemic attack, as independent determinants of stroke recurrence.^[1,13-16]

Stroke etiology is another key factor influencing recurrence risk. Recurrence rates are significantly higher in strokes caused by cardioembolic and large-vessel disease compared to those due to small-

vessel (e.g., lacunar) pathology.^[4,5] Additionally, greater baseline stroke severity (typically defined as National Institutes of Health Stroke Scale [NIHSS] score ≥ 4) was associated with an elevated risk of recurrence. These findings reinforce the importance of individualized secondary prevention strategies, which should be updated dynamically based on patient risk profiles.^[12,15]

Despite these insights, the literature reveals a need for large-scale, long-term, multicenter studies to facilitate early identification of patients at risk for recurrence and to support the development of personalized follow-up protocols. In countries such as Türkiye, characterized by heterogeneity in socioeconomic status and healthcare access, such studies are limited.^[5] This gap presents a challenge not only for clinical decision-making but also for informing national healthcare policy.

This study utilized a multicenter cohort drawn from 11 tertiary centers across different regions of Türkiye. The same dataset was previously analyzed by Kunt et al.^[17] in a study investigating determinants of early mortality (within the first 30 days), identifying factors such as elevated NIHSS and modified Rankin Scale (mRS) scores, hyperglycemia, and thyroid disease as being significantly associated with mortality. In contrast, the current analysis focused specifically on stroke recurrence as a distinct clinical endpoint. However, given the potential for shared determinants influencing both outcomes, some overlapping variables were comparatively evaluated.^[18]

The primary hypothesis of this study was that, in addition to classic vascular risk factors, certain clinical scores and biomarkers would serve as predictors of recurrence. By analyzing sociodemographic characteristics, comorbidities, laboratory values, and clinical severity scores, this study aimed to contribute to the early identification of high-risk individuals and support the personalization of secondary prevention strategies.

PATIENTS AND METHODS

The multicenter cohort study included 1,132 consecutive patients (614 males, 518 females; mean age: 70.0 ± 12.6 years) who were hospitalized with a diagnosis of acute stroke between February 2016 and December 2024 across 11 tertiary centers representing a range of rural and urban regions in Türkiye. Medical records of patients diagnosed with stroke were retrospectively reviewed. Sociodemographic and clinical characteristics

were documented. The laboratory values of the patients were analyzed within the first 24 h from the time of admission to the hospital. Exclusion criteria included a history of hematological disease, current use of immunosuppressive agents such as corticosteroids, recent infection within two weeks prior to stroke, presence of fever at initial presentation, and a history of malignancy. Although the study involved 11 tertiary centers, the sample size reflects the strict inclusion and exclusion criteria applied to ensure diagnostic accuracy and completeness of the dataset.

The diagnosis of previous stroke was based on medical documentation and neuroimaging evidence consistent with a prior cerebrovascular event. Patients were categorized according to stroke type based on neuroimaging findings. The recorded demographic data included age and sex at the time of admission to the emergency department, along with pre-existing medical conditions, smoking and alcohol use, and comorbidities such as hypertension, atrial fibrillation, hyperlipidemia, valvular heart disease, carotid artery stenosis, and dementia. Additional clinical data collected from all hospital records encompassed time from symptom onset to admission, systolic and diastolic blood pressures at presentation, blood glucose level, lipid profile, complete blood count, and transthoracic echocardiography (TTE) findings. Ischemic stroke etiology was classified according to standard categories: large artery atherosclerosis, small vessel disease, cardioembolism, other determined etiology, and undetermined etiology. Neurological status was assessed using the NIHSS and the mRS. The NIHSS scores were categorized as follows: 1-4 (mild), 5-14 (moderate), 15-20 (moderate to severe), and ≥ 21 (severe). Furthermore, mRS scores between 0-2 were categorized as mild disability, and scores between 3-5 were categorized as severe disability. Written informed consent for publication was obtained from all participants. The study protocol was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (Date: 26.02.2016, No: 92-26.02.2016). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Data analysis was performed using IBM SPSS version 22.0 software (IBM Corp, Armonk, NY, USA). The Shapiro-Wilk test was employed to assess the normality of distribution for continuous variables. Descriptive statistics were used to summarize the data. Continuous variables were

presented as means and standard deviations, while categorical variables were expressed as frequencies and percentages. For group comparisons, Student's *t*-test was used for continuous variables with normal distribution, and the Mann-Whitney U test was applied to nonnormally distributed variables. Categorical variables were compared using the chi-square test. A two-tailed *p*-value < 0.05 was considered statistically significant. In the univariate analyses, variables associated with recurrent stroke with $p < 0.05$ were considered for entry into the multivariate logistic regression model. Stroke recurrence was used as the dependent variable, and independent variables included both categorical and continuous predictors identified as significant in univariate comparisons (e.g., age, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, carotid artery stenosis, dementia, ejection fraction, hemoglobin levels, NIHSS scores, and mRS scores). The "enter" method was applied, including all eligible variables simultaneously in the model.

As this was a retrospective multicenter study, we included all consecutive eligible patients during the study period ($n = 1,132$). Therefore, no a priori power calculation was performed. However, the large sample size provided adequate power for multivariable analyses and ensured reliable estimates.

RESULTS

Among the patients, 275 (24.3%) had a history of recurrent stroke. The mean age in the recurrence group was significantly higher compared to the de novo group (73 ± 11 vs. 69 ± 13 years, $p < 0.0001$; odds ratio [OR] = 1.030). A higher proportion of patients in the recurrence group resided in rural areas (24% vs. 18%, $p = 0.017$; OR = 1.525).

With respect to cardiovascular risk factors, the recurrence group had significantly higher rates of hypertension (81% vs. 71%, $p = 0.002$; OR = 1.677), diabetes mellitus (36% vs. 29%, $p = 0.025$; OR = 1.390), atrial fibrillation (21% vs. 10%, $p < 0.0001$; OR = 2.531), hyperlipidemia (21% vs. 15%, $p = 0.010$; OR = 1.575), carotid artery stenosis (17% vs. 6%, $p < 0.0001$; OR = 3.085), valvular heart disease (12% vs. 7%, $p = 0.007$; OR = 1.855), and dementia (11% vs. 6%, $p = 0.007$; OR = 1.898). Conversely, rates of smoking (18% vs. 26%, $p = 0.008$; OR = 0.618) and alcohol use (3% vs. 8%, $p = 0.014$; OR = 0.410) were significantly lower in the recurrence group (Table 1).

In terms of clinical and laboratory findings, patients with recurrent stroke had longer hospital

TABLE 1
Demographic characteristics and comorbid diseases associated with stroke recurrence

	Recurrent stroke group (n = 275)		De novo stroke group (n = 857)		Odds ratio	95% CI	
	n	Mean ± SD	n	Mean ± SD		Lower-Upper	p
Age (year)		73 ± 11		69 ± 13	1.030		< 0.0001
Sex					0.884	0.673-1.160	0.373
Female	132		386				
Male	143		471				
Rural/urban	18/82		24/76		1.525	1.077-2.161	0.017
Smoking	17		26		0.622	0.438-0.883	0.008
Diabetes mellitus	36		29		1.390	1.042-1.854	0.025
Hypertension	81		71		1.677	1.200-2.343	0.002
Alcohol consumption	3		8		0.406	0.199-0.825	0.010
Atrial fibrillation	21		10		2.531	1.755-3.648	< 0.0001
Hyperlipidemia	21		15		1.575	1.114-2.228	0.01
Dementia	11		6		1.898	1.193-3.020	0.006
Valvular disease	12		7		1.855	1.183-2.909	0.006
Carotid stenosis	17		6		3.085	2.031-4.685	< 0.0001

CI, confidence interval; SD, standard deviation.

stays (8.9 ± 6 vs. 7.9 ± 6 days, $p = 0.038$; OR = 1.023), higher NIHSS scores (median [IQR], 5 [7.25] vs. 4 [7.00], $p = 0.011$; OR = 1.026), and higher mRS scores (median [IQR], 2 [3.00] vs. 2 [2.00], $p = 0.004$; OR = 1.135). These differences likely reflect pre-existing neurological deficits from previous strokes rather than a more severe acute presentation. Transthoracic echocardiography revealed lower mean ejection fraction (EF) values in the recurrence group (55 ± 9 vs. 59 ± 9 , $p < 0.0001$; OR = 0.963), and mean hemoglobin levels were also lower (12.5 ± 1.9 vs. 12.9 ± 1.9 g/dL, $p = 0.003$; OR = 0.892). Apart from hemoglobin, other hematological parameters, lipid profiles, and fasting glucose levels were not significant predictors of recurrent stroke. Medication use patterns were also compared between groups. Antiplatelet, anticoagulant, and statin use were all significantly more frequent among patients with recurrent stroke compared to those experiencing a first-ever event (54.6% vs. 28%, 15.8% vs. 6.8%, and 9.9% vs. 4.8%, respectively; all $p < 0.01$). Despite these differences, recurrence occurred even among patients under secondary preventive medication, suggesting that adherence, drug response, or residual vascular risk may contribute to ongoing susceptibility (Table 2).

Based on the TOAST classification, cardioembolic strokes were more prevalent in

the recurrence group, while lacunar strokes were less common ($p < 0.0001$). No significant differences were observed between groups for other laboratory parameters, including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and fasting blood glucose levels, and neutrophil and lymphocyte counts ($p > 0.05$ for all). The 30-day mortality rates were 10.5% in the recurrence group and 6.8% in the de novo stroke group, representing a difference that approached but did not reach statistical significance ($p = 0.053$; OR = 0.628; Table 2).

In multivariate logistic regression analysis, age and carotid artery stenosis emerged as the only independent predictors of ischemic stroke recurrence. Each one-year increase in age was associated with a 3.8% higher odds of recurrence (OR = 1.038, $p = 0.003$). The presence of carotid artery stenosis was associated with a more than two-fold increase in recurrence risk (OR = 2.608, $p = 0.004$). In contrast, several variables that were significant in univariate comparisons, including hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, dementia, and valvular heart disease, did not retain statistical significance after adjustment for potential confounders. These findings indicate that the associations observed in the descriptive analyses (Tables 1 and 2) are largely explained by the strong independent effects of

TABLE 2
Laboratory and clinical markers at admission and discharge associated with stroke recurrence

	Recurrent stroke group (n = 275)			De novo stroke group (n = 857)			Odds ratio	95% CI		p
	%	Mean ± SD	Median	IQR	%	Mean ± SD		Median	IQR	
Length of stay (day)		8.9 ± 6			7.9 ± 6		1.023	1.001-1.046	0.038	
SBP at admission (mmHg)		153 ± 26			152 ± 25		1.002	0.996-1.009	0.468	
DBP at admission (mmHg)		86 ± 13			85 ± 12		1.007	0.995-1.021	0.255	
LDL cholesterol (mg/dL)		126 ± 35			126 ± 38		1.000	0.996-1.004	0.896	
HDL cholesterol (mg/dL)		42 ± 10			43 ± 11		0.989	0.975-1.003	0.115	
FBG (mg/dL)		145 ± 70			146 ± 70		1.000	0.998-1.002	0.789	
TTE-EF (%)		55 ± 9			59 ± 9		0.963	0.948-0.979	< 0.0001	
Neutrophil ×10 ³ /μL		6.1 ± 2			5.9 ± 2		1.017	0.964-1.072	0.541	
Lymphocyte ×10 ³		2.2 ± 1.1			2.2 ± 1		0.992	0.872-1.128	0.898	
Hemoglobin (g/dL)		12.5 ± 1.9			12.9 ± 1.9		0.892	0.827-0.961	0.003	
Antiplatelet use	54.6						3.089	2.332-4.092	0.0001	
Anticoagulant use	15.8			28.0			2.575	1.691-3.923	0.0001	
Statin use	9.9			4.8			2.174	1.310-3.606	0.002	
Stroke subtypes							0.969	0.751-1.251	0.651	
Ischemic	86			85						
Hemorrhagic	8			9						
TIA	6			6						
TOAST									0.007	
Large artery	8			13						
Cardioembolism	22			14						
Lacunar infarcts	37			42						
Others	1			0.3						
Undetermined	31			30						
NIHSS		5	7.25		4	7.00	1.026	1.006-1.047	0.011	
mRS		2	3.00		2	2.00	1.135	1.040-1.238	0.004	
30-day mortality	10.50			6.8			0.628	0.393-1.006	0.053	

CI, confidence interval; SD, standard deviation; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; FBG, fasting blood glucose; TTE-EF, transthoracic echocardiography ejection fraction; TIA, transient ischemic attack; TOAST, trial of org 10172 in acute stroke treatment; NIHSS, National Institutes of Health Stroke Scale; mRS, Modified Rankin Scale.

TABLE 3
The effects of variables in the multiple logistic regression model on stroke recurrence

Variables	β	SE	Wald	df	<i>p</i>	Exp (β)
Age (year)	0.037	0.012	9.002	1	0.003	1.038
Rural/urban (%)	0.285	0.251	1.282	1	0.258	1.329
Smoking	0.063	0.274	0.053	1	0.819	1.065
Alcohol consumption	-0.572	0.465	1.513	1	0.219	0.565
TTE-EF (%)	-0.012	0.011	1.349	1	0.245	0.988
Atrial fibrillation	0.383	0.344	1.242	1	0.265	1.466
Hypertension	0.275	0.232	1.396	1	0.237	1.316
Hyperlipidemia	0.076	0.288	0.70	1	0.791	1.079
Diabetes mellitus	0.172	0.212	0.655	1	0.418	1.187
Valvular disease	-0.508	0.359	2.001	1	0.157	0.601
Carotid stenosis	0.959	0.333	8.282	1	0.004	2.608
Dementia	-0.107	0.330	0.106	1	0.745	0.898

SE, standard error; Exp, exponential; TTE-EF, transthoracic echocardiography-ejection fraction.

age and carotid artery stenosis in the multivariate model (Table 3). When the analysis was repeated after excluding patients who died within 30 days of index stroke, multivariate regression identified age ($B = 0.023$, $p = 0.006$; $OR = 1.023$), carotid artery stenosis ($B = 0.878$, $p = 0.007$; $OR = 2.407$), and reduced EF on TTE ($B = 0.028$, $p = 0.005$; $OR = 0.973$) as significant predictors of recurrence.

In our previous analysis of the same cohort, early (first 30 days) mortality was significantly associated with elevated blood glucose ($OR = 1.01$), higher NIHSS ($OR = 1.24$) and mRS scores ($OR = 4.23$), and thyroid disease ($OR = 8.04$).^[17] In the current study, reanalysis of these parameters, excluding mortality, showed that age, carotid artery stenosis, and low EF on TTE remained significant predictors of recurrence. These findings suggest that while certain determinants may influence both endpoints, stroke recurrence and early mortality are shaped by partially distinct clinical risk profiles.

DISCUSSION

The most notable finding of this multicenter cohort study was that increasing age and the presence of carotid artery stenosis emerged as independent predictors of stroke recurrence.^[3,4] These two variables retained their significance in the multivariate analysis, distinguishing them from other factors that were only significant in univariate comparisons.^[1,5] The findings mostly align with trends reported in the current literature.

Amarenco et al.^[4] found a five-year recurrence rate of 11% and identified age, hypertension, diabetes mellitus, cardiac disease, and carotid pathology as key predictors. Similarly, Lambert et al.^[3] demonstrated that vascular markers such as age and carotid pathology were strongly associated with recurrence. Kolmos et al.^[1] also emphasized the role of cardioembolic etiology, hypertension, and atrial fibrillation as significant risk factors for recurrent events. The significant association found in our study between cardioembolic stroke subtypes in the TOAST classification and recurrence risk is consistent with the abovementioned data. Cardioembolic strokes are typically more aggressive and may recur despite secondary preventive measures, as reported in other studies.^[19] However, some of our findings diverge from prior research. For instance, in a systematic review and meta-analysis, Mohan et al.^[20] identified diabetes as a consistent independent determinant of stroke recurrence across multiple cohorts, but this association did not persist in the multivariate model in our study. Similarly, despite the widely recognized role of atrial fibrillation as a risk factor,^[21] it did not emerge as an independent predictor in our final analysis. These discrepancies may be attributed to differences in cohort characteristics, follow-up duration, treatment protocols, antithrombotic use, or heterogeneity in diagnostic approaches.

In addition to these international findings, evidence from a recent study by Dinç et al.^[22] supports the central role of carotid artery disease

in stroke recurrence. In their cohort of patients with minor ischemic stroke, the most significant predictors of early recurrent events were coronary artery disease and, notably, asymptomatic internal carotid artery stenosis. These results align with our observation that carotid stenosis emerged as an independent determinant of recurrence in a large nationwide multicenter cohort. Taken together, these data underscore the importance of aggressive evaluation and management of carotid atherosclerosis within secondary prevention strategies. These findings also support the role of early vascular imaging and systematic evaluation of carotid artery disease as part of comprehensive secondary stroke prevention strategies.

While our previous analysis of the same patient cohort identified elevated NIHSS and mRS scores, hyperglycemia, and thyroid disease^[17] as being determinants of early mortality, the present study focuses exclusively on recurrence, allowing for a comparative evaluation of shared and distinct predictors across these two critical endpoints. The relatively low 30-day mortality rate in the recurrence group (10.5%), consistent with some previous reports, suggests that recurrent strokes may not always be associated with more severe clinical outcomes. Previous research has highlighted clinical variables that primarily drive early mortality, including high NIHSS scores, advanced age, impaired consciousness, and hyperglycemia, while also showing that timely reperfusion therapies significantly reduce early fatality.^[23] In contrast, Kristensen et al.^[24] reported that in patients with type 2 diabetes mellitus, recurrence and mortality risks diverged, likely due to diabetes-related microvascular damage and chronic inflammation. Similarly, although diabetes was more prevalent among patients with recurrence in our cohort, it did not reach statistical significance in the multivariate model. These findings suggest that the relationship between recurrence and mortality is not direct but rather shaped by etiological and individual factors. Therefore, secondary prevention should be multidimensional, addressing both recurrence and mortality risk concurrently. Although higher NIHSS and mRS scores were observed among patients with recurrent stroke, this may be partially attributable to residual deficits from previous cerebrovascular events rather than the severity of the acute index episode itself. The higher prevalence of antiplatelet, anticoagulant, and statin use among patients with recurrent stroke indicates that pharmacological secondary prevention alone may not be sufficient to eliminate

recurrence risk. This finding aligns with previous studies emphasizing that recurrence often occurs despite optimal medical therapy, underscoring the multifactorial nature of stroke recurrence. Potential contributors include suboptimal adherence, treatment resistance, unaddressed vascular comorbidities, or inadequate control of modifiable risk factors. However, because detailed information on treatment adherence, dosage, and treatment duration was not available in the dataset, it was not possible to determine whether recurrent events represented true treatment failure or suboptimal adherence. These results highlight the need for individualized, multimodal strategies that extend beyond pharmacologic measures.

The absence of a significant association between smoking and stroke recurrence in our study aligns with discussions around the so-called “smoking paradox.” Several studies have reported better outcomes and lower mortality in smokers following intravenous thrombolysis,^[25] although these benefits are often attributed to factors such as younger age, fewer comorbidities, and lower baseline NIHSS scores among smokers.^[15,26] Adjusted analyses demonstrated that this advantage typically disappeared, suggesting that smoking does not have a direct protective effect on clinical outcomes.^[27] Moreover, poststroke smoking cessation may weaken its long-term effect on recurrence. Cigarette smoking does not have a significant effect on recurrence, which suggests that this variable should be evaluated in conjunction with factors such as individual health profile and stroke severity. Lower smoking prevalence in the recurrence group should, therefore, not be interpreted as a protective effect of smoking, but rather as a reflection of behavioral changes after the first cerebrovascular event, particularly smoking cessation.

In clinical practice, smoking should not be interpreted as a positive prognostic indicator but as a strong cerebrovascular risk factor. Feigin et al.^[2] highlighted that recurrent strokes substantially contributed to the global burden of cerebrovascular disease and exacerbated long-term disability and quality-of-life impairments, underscoring the need for early detection of modifiable risk factors and targeted intervention strategies. The prominence of age and carotid artery stenosis as predictors highlights the importance of closely monitoring elderly individuals and considering more aggressive management strategies for patients with carotid pathology, including endovascular intervention.

Incorporating vascular imaging findings into routine poststroke risk stratification may facilitate earlier identification of high-risk individuals and support more individualized secondary prevention strategies. Prior studies reported that recurrence risk was substantially elevated in individuals with carotid stenosis and that carotid stenting or endarterectomy may significantly reduce recurrence.^[28,29] Our findings highlight that stroke recurrence may persist despite pharmacological secondary prevention, emphasizing the importance of therapy adherence monitoring and complementary lifestyle-based interventions.

Future research should aim to capture prospective, long-term data on secondary prevention strategies, including monitoring of adherence to antithrombotic and lipid-lowering therapies, blood pressure and lipid management, and the impact of lifestyle modifications on recurrence risk. Standardized diagnostic approaches (e.g., uniform use of transesophageal echocardiography *vs.* TTE for cardioembolic sources) across centers will help reduce heterogeneity and improve comparability of results. In addition, time-dependent analyses of recurrence are warranted to determine whether predictors such as diabetes or atrial fibrillation exert stronger effects across early and late poststroke phases.^[20,21] There is also a need to incorporate novel risk prediction models that combine traditional vascular risk factors with laboratory biomarkers and imaging parameters, which may enhance individualized risk stratification.^[15,16] The integration of digital health technologies, including wearable devices and mobile applications, may further facilitate real-time monitoring of adherence and early detection of recurrence-prone individuals. Further studies should also examine the impact of antihypertensive and antidiabetic medication use, which were not included in the present dataset, on long-term recurrence risk.

Finally, international multicenter cohorts with diverse populations are essential to validate findings across healthcare systems and ethnic groups. Such efforts will inform not only clinical practice but also healthcare policy planning, aiming to reduce the global burden of recurrent stroke.^[2] Integration of clinical, imaging, and biomarker-based risk models may further improve the prediction of recurrent stroke in large multicenter cohorts.

This study contributed to the literature by examining potentially modifiable determinants of stroke recurrence in a large, homogeneous,

multicenter cohort. However, the retrospective design and the reliance on acute-phase data limited the ability to evaluate long-term secondary prevention strategies. As a result, information regarding treatment adherence, lifestyle modifications, and follow-up care was not available. Another limitation was the lack of standardization in diagnostic work-up across participating centers. The use of TTE and transesophageal echocardiography for the evaluation of potential cardioembolic sources varied between institutions. This heterogeneity may have contributed to the relatively high proportion of strokes classified as undetermined etiology and should be considered when interpreting etiological distributions. In addition, patients with recent infection or immunosuppressive therapy were excluded to avoid confounding conditions such as encephalitis, cerebral abscess, or systemic inflammatory encephalopathies that may mimic stroke-related findings. However, this exclusion also limited the ability to evaluate the potential contribution of systemic inflammatory processes to stroke recurrence. Another limitation was the lack of detailed etiological classification of the index stroke in patients who experienced recurrent events. Consequently, concordance between the etiologies of the index and recurrent strokes could not be analyzed. Nonetheless, several factors strengthened the validity of the present findings. The multicenter design, the relatively large sample size, and the specific focus on recurrence (separate from early mortality) enhanced the generalizability and clinical relevance of the results.

Current evidence indicates that carefully selected patients may benefit from timely carotid revascularization in addition to optimal medical therapy. Contemporary guidelines recommend that carotid endarterectomy be considered for symptomatic stenosis $\geq 50\text{-}70\%$ and performed as soon as patients are neurologically stable, ideally within two weeks of the index ischemic event. Although perioperative risk may increase modestly with age, recurrence risk under medical therapy alone rises substantially in older individuals, suggesting that appropriately selected elderly patients may derive meaningful benefit from timely intervention and aggressive vascular risk-factor control.^[30-33] Our findings reinforce the need for early identification of high-risk patients and support the integration of vascular imaging and individualized risk profiling into routine secondary stroke prevention strategies.

In conclusion, advanced age and carotid artery stenosis emerged as the most robust independent predictors of recurrent ischemic stroke in this nationwide multicenter cohort. These findings emphasize the importance of individualized vascular risk profiling and early identification of patients with clinically significant carotid disease. Carotid stenosis represents a major determinant of stroke recurrence, particularly in symptomatic patients with moderate-to-severe stenosis.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: N.G.B., B.P.Ç., R.K., S.K.: Idea/concept, design, analysis and/or interpretation, literature review; B.P.Ç., M.F.Ö., S.K.: Control/supervision, critical review; N.G.B., B.P.Ç., R.K., B.Y., H.G., İ.S., S.Ç.U., E.Ö.G., B.Y., D.Ö., A.O.K., O.K., Ç.K.A., V.S., M.A., F.Z.A., Z.E., M.E., M.M.A., S.K., M.F.Ö.: Data collection and/or processing; N.G.B., B.P.Ç., S.K.: Writing the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

AI Disclosure: The authors declare that artificial intelligence (AI) tools were not used, or were used solely for language editing, and had no role in data analysis, interpretation, or the formulation of conclusions. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors. The authors further confirm that AI tools were not used to generate, fabricate, or ‘hallucinate’ references, and that all references have been carefully verified for accuracy.

REFERENCES

- Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke - A systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2021;30:105935. doi: 10.1016/j.jstrokecerebrovasdis.2021.105935.
- Feigin VL, Stark BA, Johnson CO, GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021;20:795-820. doi: 10.1016/S1474-4422(21)00252-0.
- Lambert CM, Olulana O, Bailey-Davis L, Abedi V, Zand R. “Lessons Learned” preventing recurrent ischemic strokes through secondary prevention programs: A systematic review. *J Clin Med* 2021;10:4209. doi: 10.3390/jcm10184209.
- Amarenco P, Lavallée PC, Monteiro Tavares L, Labreuche J, Albers GW, Abboud H, et al. Five-year risk of stroke after TIA or minor ischemic stroke. *N Engl J Med* 2018;378:2182-90. doi: 10.1056/NEJMoa1802712.
- Arsava EM, Kim GM, Oliveira-Filho J, Gungor L, Noh HJ, Lordelo Mde J, et al. Prediction of early recurrence after acute ischemic stroke. *JAMA Neurol* 2016;73:396-401. doi: 10.1001/jamaneurol.2015.4949.
- Marnane M, Ni Chroinin D, Callaly E, Sheehan OC, Merwick A, Hannon N, et al. Stroke recurrence within the time window recommended for carotid endarterectomy. *Neurology* 2011;77:738-43. doi: 10.1212/WNL.0b013e31822b00cf.
- Wang Y, Xu J, Zhao X, Wang D, Wang C, Liu L, et al. Association of hypertension with stroke recurrence depends on ischemic stroke subtype. *Stroke* 2013;44:1232-7. doi: 10.1161/STROKEAHA.111.000302.
- 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:e007267. doi: 10.1161/JAHA.117.007267.
- Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35-41. doi: 10.1161/01.str.24.1.35.
- Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. *Stroke* 2001;32:2735-40. doi: 10.1161/hs1201.100209.
- Cabral NL, Muller M, Franco SC, Longo A, Moro C, Nagel V, et al. Three-year survival and recurrence after first-ever stroke: The Joinville stroke registry. *BMC Neurol* 2015;15:70. doi: 10.1186/s12883-015-0317-1.
- Lee SH, Jung JM, Ryu JC, Park MH. Variations in risk factors across different periods of stroke and transient ischemic attack recurrence. *Eur Neurol* 2024;87:213-22. doi: 10.1159/000540571.
- Demirci S, Yalçın BZ, Bakaç G, Dayan C, Aysal F, Baybaş S. Risk Factors that affect stroke recurrence. *Dusunen Adam J Psychiatr Neurol Sci* 2010;23:38-43. doi: 10.5350/DAJPN2010230106t.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665. doi: 10.1136/bmj.b1665.
- Liang X, Cheng L, Zhang S, Yuan D, Hou Y. Analysis of risk factors for recurrence of patients with ischemic stroke and construction of risk prediction model. *Minerva Med* 2023;114:571-3. doi: 10.23736/S0026-4806.21.07620-5.
- Ke L, Zhang H, Long K, Peng Z, Huang Y, Ma X, et al. Risk factors and prediction models for recurrent acute ischemic stroke: A retrospective analysis. *PeerJ* 2024;12:e18605. doi: 10.7717/peerj.18605.
- Kunt R, Çınar BP, Yüksel B, Güllüoğlu H, Sayılır İ, Çeliker Uslu S, et al. Clinical-epidemiological and radiological characteristics of stroke patients: A multicentre study. *Int J Clin Pract* 2021;75:e14963. doi: 10.1111/ijcp.14963

18. McCabe JJ, Walsh C, Gorey S, Harris K, Hervella P, Iglesias-Rey R, et al. Plasma fibrinogen and risk of vascular recurrence after ischaemic stroke: An individual participant and summary-level data meta-analysis of 11 prospective studies. *Eur Stroke J* 2024;9:704-13. doi: 10.1177/23969873241246489.
19. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010;6:150-61. doi: 10.2174/157340310791658730.
20. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, et al. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. *Stroke* 2011;42:1489-94. doi: 10.1161/STROKEAHA.110.602615.
21. Wong ZY, Yuen LZH, Tan YK, Goh CXY, Teo YN, Ho JSY, et al. Detection of atrial fibrillation after ischemic stroke with an insertable cardiac monitor: A systematic review and individual patient data meta-analysis of randomized clinical trials. *Cerebrovasc Dis* 2024;53:316-26. doi: 10.1159/000533265.
22. Dinç Y, Oğuz Akarsu E, Hakyemez B, Bakar M. Evaluation of risk factors associated with stroke recurrence in patients with minor ischemic stroke. *Turk J Neurol* 2022;28:14-8. doi: 10.4274/tnd.2021.17992.
23. Nedeltchev K, Renz N, Karameshev A, Haefeli T, Brekenfeld C, Meier N, et al. Predictors of early mortality after acute ischaemic stroke. *Swiss Med Wkly* 2010;140:254-9. doi: 10.4414/smw.2010.12919.
24. Kristensen FPB, Svane HML, Laugesen K, Al-Mashhadi SK, Christensen DH, Sørensen HT, et al. Risk of mortality and recurrence after first-time stroke among patients with type 2 diabetes: A Danish nationwide cohort study. *Eur Stroke J* 2025;10:190-7. doi: 10.1177/23969873241260956.
25. Kurmann R, Engelter ST, Michel P, Luft AR, Wegener S, Branscheidt M, et al. Impact of smoking on clinical outcome and recanalization after intravenous thrombolysis for stroke: Multicenter cohort study. *Stroke* 2018;49:1170-5. doi: 10.1161/STROKEAHA.117.017976.
26. Wang HK, Huang CY, Sun YT, Li JY, Chen CH, Sun Y, et al. Smoking paradox in stroke survivors?: Uncovering the truth by interpreting 2 sets of data. *Stroke* 2020;51:1248-56. doi: 10.1161/STROKEAHA.119.027012.
27. Zafar F, Wadhwa A, Kumar K, Ahmed M, Khokhar AS, Sajjad S, et al. Smoke signals: Unraveling the paradoxical impact of smoking on stroke prognosis and treatment efficacy. *Cureus* 2024;16:e52346. doi: 10.7759/cureus.52346.
28. Strömberg S, Nordanstig A, Bentzel T, Österberg K, Bergström GM. Risk of early recurrent stroke in symptomatic carotid stenosis. *Eur J Vasc Endovasc Surg* 2015;49:137-44. doi: 10.1016/j.ejvs.2014.11.004.
29. Abbott AL. Extra-cranial carotid artery stenosis: An objective analysis of the available evidence. *Front Neurol* 2022;13:739999. doi: 10.3389/fneur.2022.739999.
30. Leung YYR, Bera K, Urriza Rodriguez D, Dardik A, Mas JL, Simonte G, et al. Safety of carotid endarterectomy for symptomatic stenosis by age: Meta-analysis with individual patient data. *Stroke* 2023;54:457-67. doi: 10.1161/STROKEAHA.122.040819.
31. Messas E, Goudot G, Halliday A, Sitruk J, Mirault T, Khider L, et al. Management of carotid stenosis for primary and secondary prevention of stroke: State-of-the-art 2020: a critical review. *Eur Heart J Suppl* 2020;22:M35-42. doi: 10.1093/eurheartj/suaa162.
32. Bonati LH, Kakkos S, Berkefeld J, de Borst GJ, Bulbulia R, Halliday A, et al. European Stroke Organisation guideline on endarterectomy and stenting for carotid artery stenosis. *Eur Stroke J* 2021;6:I-XLVII. doi: 10.1177/23969873211012121.
33. AbuRahma AF, Avgerinos ED, Chang RW, Darling RC 3rd, Duncan AA, Forbes TL, et al. Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *J Vasc Surg* 2022;75:4S-22. doi: 10.1016/j.jvs.2021.04.073.