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Is left atrial diameter related to ischemic stroke?

Sol atrium çapı iskemik inme ile ilişkili midir?

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Abstract

Purpose: Stroke is the second leading cause of death and the third leading cause of disability worldwide. The highest recurrence rates are observed in subtypes such as large artery atherosclerosis (LAA) and cardioembolic (CE) stroke. Atrial fibrillation (AF) is a common cause of CE. However, the role of increased left atrial (LA) size as a potential risk factor for ischemic stroke remains controversial. This study aimed to evaluate whether LA size is associated with the long-term risk of stroke recurrence in patients with non-valvular atrial fibrillation.

Materials and methods: This retrospective study included 191 patients diagnosed with ischemic stroke by a specialist neurologist at Afyonkarahisar University of Health Sciences between January 1, 2024, and June 1, 2024. Patients aged >18 years with acute ischemic stroke were included. Patients with a history of ischemic stroke who had not undergone transthoracic echocardiography were excluded. The etiological subtype of ischemic stroke was determined according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.

Results: A total of 191 patients were included. Of these, 155 (81.2%) had non-recurrent stroke, while 36 (18.8%) experienced recurrent stroke. Smoking was significantly more common in patients with recurrent ischemic stroke (30.6% vs. 16.1%; p=0.046). The prevalence of AF was also higher in the recurrent stroke group (33.3% vs. 12.9%; p=0.003). Moreover, LA diameter was significantly greater in patients with recurrent ischemic stroke (median [interquartile range]: 43 [35.75-47] vs. 35 [33-37]; p<0.001).

Conclusion: This study demonstrates that increased LA diameter, smoking, and AF are associated with a higher risk of recurrent ischemic stroke. Notably, larger LA diameter may contribute to blood stasis and thrombus formation in the left atrium, thereby elevating the risk of CE events. Further research is warranted to confirm these associations and strengthen the current evidence base.

Keywords: Atrial fibrillation, ischemic stroke, LA diameter.

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Öz

Amaç: İnme, dünya çapında ikinci en sık ölüm nedeni ve üçüncü en sık sakatlık nedenidir. En yüksek nüks oranları büyük arter aterosklerozu ve kardiyoembolik inme gibi alt tiplerde görülmektedir. Atriyal fibrilasyon kardiyoembolik inmenin yaygın bir nedenidir. Ancak sol atriyum çapındaki artışın iskemik inme için potansiyel bir risk faktörü olup olmadığı tartışmalıdır. Bu çalışmanın amacı, sol atriyum çapının kapak hastalığına bağlı olmayan atriyal fibrilasyonu olan hastalarda uzun dönem inme tekrarı riski ile ilişkili olup olmadığını değerlendirmektir.

Gereç ve yöntem: Bu retrospektif çalışmaya, 1 Ocak 2024 ile 1 Haziran 2024 tarihleri arasında Afyonkarahisar Sağlık Bilimleri Üniversitesi'nde uzman nörolog tarafından iskemik inme tanısı konulan 191 hasta dahil edildi. Dahil edilme kriterleri 18 yaş üzeri olup akut iskemik inme tanısı alan hastalardı. Önceden inme öyküsü olan ancak transtorasik ekokardiyografi yapılmamış hastalar çalışma dışında bırakıldı. İskemik inmenin etiyolojik alt tipi TOAST (Trial of Org 10172 in Acute Stroke Treatment) kriterlerine göre belirlendi.

Bulgular: Çalışmaya toplam 191 hasta dahil edildi. Bunların 155'i (%81,2) tekrarlamayan inme grubunda, 36'sı (%18,8) ise tekrarlayan inme grubundaydı. Sigara kullanımı, tekrarlayan inme grubunda anlamlı olarak daha yüksekti (%30,6'ya karşı %16,1; p=0,046). Atriyal fibrilasyon sıklığı da tekrarlayan inme grubunda daha fazlaydı (%33,3'e karşı %12,9; p=0,003). Ayrıca, sol atriyum çapı tekrarlayan iskemik inme hastalarında anlamlı derecede daha büyüktü (ortanca [çeyrekler arası aralık]: 43 [35,75-47] mm'ye karşı 35 [33-37] mm; p<0,001).

Sonuç: Bu çalışma, sol atriyum çapındaki artışın, sigara kullanımının ve atriyal fibrilasyonun tekrarlayan iskemik inme riski ile ilişkili olduğunu göstermektedir. Özellikle sol atriyum çapındaki genişleme, atriyumda kan stazı ve trombüs oluşumuna katkıda bulunarak kardiyoembolik olay riskini artırabilir. Bu ilişkilerin doğrulanması ve mevcut kanıtların güçlendirilmesi için ileri çalışmalara ihtiyaç vardır.

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Anahtar kelimeler: Atriyal fibrilasyon, iskemik inme, sol atriyum çapı.

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Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide [1]. The primary risk factor for acute ischemic stroke is high BP. Other conditions that increase stroke risk include a history of transient ischemic attack (TIA), smoking, high cholesterol, diabetes, obesity, end-stage renal disease, and AF [2]. Although marked improvements have been achieved in neuroimaging, acute stroke care, and secondary prevention, recurrent ischemic stroke remains a prominent clinical problem [3]. Despite the increased implementation of secondary prevention strategies over the past two decades, the incidence of recurrent ischemic stroke has remained largely unchanged [4, 5]. The highest recurrence rates are seen in LAA and CE stroke subtypes [6]. Some studies have identified hypertension (HT) and diabetes mellitus (DM) as predictors of stroke recurrence [7, 8], although this association has not been consistently demonstrated [9, 10]. Additionally, AF [7], chest pain [10], ischemic heart disease [7], and cardiomyopathy [11] have been reported as independent risk factors for stroke recurrence, but not all studies agree on the role of AF as a risk factor [10]. The impact of increased atrial size as a potential risk factor for ischemic stroke is debated; some studies support this association [12, 13], while others do not [14, 15]. Despite various assessment methods, the role of atrial size in stroke remains controversial. This study aimed to determine the relationship between left atrial diameter (LAD) and the risk of recurrent ischemic stroke.

Materials and methods

This study was a retrospective analysis conducted by reviewing the medical records of patients admitted to the Neurology Department of Afyonkarahisar Health Sciences University Hospital between January 1, 2024, and June 1, 2024. It included 191 patients diagnosed with ischemic stroke by a specialist neurologist at Afyonkarahisar Health Sciences University. Inclusion criteria were patients over the age of 18 diagnosed with acute ischemic stroke. Patients with a history of prior ischemic stroke who had not undergone transthoracic echocardiography were excluded. Ischemic stroke was diagnosed using brain imaging methods, including 1.5 Tesla magnetic resonance imaging (MRI) and diffusion-weighted imaging (DWI), alongside computed tomography (CT), in combination with clinical findings. Patients with tuberculous meningitis, brain tumors, viral or bacterial encephalitis, multiple sclerosis, and hemorrhagic stroke were also excluded from the study. The etiologic subtype of ischemic stroke was classified according to the TOAST criteria. This classification includes the following subgroups: 1) Large vessel atherosclerosis 2) Cardiac embolism 3) Small vessel disease (lacunar infarct) 4) Other determined etiology: hematologic causes, coagulopathies, thrombocytosis, polycythemia, deficiency of coagulation inhibitors, antiphospholipid antibody syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and other causes of cerebrovascular disease not listed above 5) Stroke of undetermined etiology (ESUS) [16].

Approval for this study was obtained from the Ethics Committee of Afyonkarahisar Health Sciences University Faculty of Medicine (approval date: August 2, 2024; decision no: 2024/6; appendix-1). Due to the retrospective nature of the study, informed consent was not obtained from the included individuals.

Clinical data

Baseline data were recorded for all patients, including demographic, clinical, echocardiographic, and medication information. Risk factors assessed included age, sex, blood pressure (BP) measurements, smoking history, alcohol consumption history, past history of stroke, and the use of antidiabetic, antihypertensive, or antihyperlipidemic drugs.

- HT was defined as either the use of antihypertensive medication or a history of diagnosed HT with a reported systolic BP of 140 mmHg or higher and/or a diastolic BP of 90 mmHg or higher.
- DM was defined by fasting serum glucose levels ≥126 mg/dL (7 mmol/L), non-fasting glucose levels ≥200 mg/dL (11.1 mmol/L), use of diabetic medication, or a previously established diagnosis of diabetes.
- Hyperlipidemia (HL) was defined as having LDL-cholesterol levels ≥130 mg/dL (3.37 mmol/L), total cholesterol levels ≥200 mg/dL (5.18 mmol/L), or the use of lipid-lowering agents following a diagnosis of HL [17].
- AF was defined as AF recorded during electrocardiography ,48-hour holter monitoring record or any known previous episode.
- Smoking and alcohol consumption were classified as current or former use.
- The diagnosis of carotid stenosis was established using Doppler ultrasound, contrast-enhanced CT angiography, and non-contrast MR angiography.
- Medications, including the use of antiplatelet or anticoagulation agents, were recorded at discharge.

Echocardiography measurements

Transthoracic echocardiography was performed in the left lateral decubitus position using standard imaging planes, following the recommendations of the American Society of Echocardiography. LAD was measured using two-dimensional echocardiography from the posterior aortic wall to the posterior left atrial wall in the parasternal long-axis view at end-ventricular systole. LAD is a commonly used echocardiographic parameter for assessing left atrial size [18]. Measurements were recorded from echocardiography reports.

Left atrial size was categorized into four groups based on LAD and sex:

- **Normal left atrial size:** Women ≤38 mm, Men ≤40 mm
- **Mild left atrial size:** Women 39-42 mm, Men 41-46 mm
- **Moderate left atrial size:** Women 43-46 mm, Men 47-51 mm
- **Severe left atrial size:** Women ≥47 mm, Men ≥52 mm [14, 19].

Statistical methods

Statistical analyses were performed using SPSS 26.0 (IBM Corp., 2019, IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp). Categorical variables were presented as percentages and frequencies and compared using the Chi-Square test. Continuous variables that were not normally distributed were expressed as median (interquartile range) and analyzed using the Mann-Whitney U test. Logistic regression analysis was conducted to identify factors associated with recurrent ischemic stroke, using three different models.

Model 1: A basic model evaluating the effect of LAD on recurrent ischemic stroke.

Model 2: A model including age and gender.

Model 3: A fully adjusted model including age, gender, smoking, alcohol consumption, HT, diabetes mellitus, HL, heart failure, carotid atherosclerosis, and atrial fibrillation.

A significance level of $p<0.05$ was considered statistically significant for all analyses. The results were reported as odds ratios (OR) with 95% confidence intervals (CI).

Model 1. A basic model evaluating the effect of LA diameter on recurrent ischemic stroke

Variables	*p* value	O.R	95% C.I.for O.R	
			Lower	Upper
LA diameter	0.000*	1.159	1.094	1.229
Constant	0.000*	0.001		

LA: Left atrium, OR: Odds Ratio, *:This was statistically significant $p<0.05$

Model 2. A model including age and gender

Variables	*p* value	O.R	95% C.I.for O.R	
			Lower	Upper
LA diameter	0.000*	1.166	1.096	1.241
Age	0.612	0.992	0.960	1.024
Gender	0.672	0.834	0.360	1.931
Constant	0.000*	0.001		

LA: Left atrium, OR: Odds Ratio, *:This was statistically significant $p<0.05$

Model 3. A fully adjusted model including age, gender, smoking, alcohol consumption, hypertension, diabetes mellitus, hyperlipidemia, heart failure, carotid atherosclerosis, and atrial fibrillation

Variables	*p* value	O.R	95% C.I.for O.R	
			Lower	Upper
Age	0.212	0.976	0.939	1.014
Male	0.032*	0.190	0.042	0.867
Smoking	0.013*	0.158	0.037	0.677
Alcohol consumption	0.560	0.422	0.023	7.674
Hypertension	0.430	1.451	0.576	3.654
Diabetes Mellitus	0.291	1.669	0.645	4.316
Hyperlipidemia	0.741	0.797	0.207	3.067
Heart failure	0.721	1.303	0.304	5.594
Carotid Atherosclerosis	0.040*	3.169	1.056	9.514
Atrial fibrilation	0.086	3.677	0.830	16.287
LA diameter	0.000*	1.176	1.088	1.271
Constant	0.007*	0.006		

LA: Left atrium, OR: Odds Ratio, *:This was statistically significant $p<0.05$

Results

Demographic characteristics

A total of 191 patients were included in the study. Of these, 75 patients (39.3%) were female and 116 patients (60.7%) were male. The median age of all patients was 69 years; the median age for women was 68 years, and for men, it was 69 years.

In terms of lifestyle and medical history:

- 36 patients (18.8%) were smokers.
- 5 patients (2.6%) were alcohol users.
- 145 patients (75.9%) had a history of chronic disease.
- 73 patients (83.2%) had HT.
- 78 patients (40.8%) had DM.
- 31 patients (16.2%) had HL.
- 16 patients (8.4%) had heart failure (HF).

Carotid stenosis of 50% or more was detected in 87 patients (45.5%).

Clinical and demographic characteristics of all patients are detailed in Table 1.

Among the study population:

- 155 patients (81.2%) had non-recurrent stroke.
- 36 patients (18.8%) had recurrent stroke.

Table 1 presents a comparison of the findings between non-recurrent and recurrent stroke cases. Smoking was significantly more common in patients with recurrent ischemic stroke (30.6% vs. 16.1%; *p*=0.046). Additionally, the prevalence of AF was significantly higher in the recurrent stroke group (33.3% vs. 12.9%; *p*=0.003).

Table 1. Comparisons of clinical and demographic characteristics of patients with recurrent and nonrecurrent ischemic stroke

Characteristic	Total (n:191)	Non-recurrent CVD (n:155)	Recurrent CVD (n:36)	*p*
Age(year)	68 (60-75)	69 (60-78)	69.5 (60.25-76.75)	0.977 (z=-0.028)
Gender (male)	116 (60.7)	96 (61.9)	20 (55.6)	0.480 (cs=0.499)
Smokers	36 (18.8)	25 (16.1)	11 (30.6)	0.046* (cs=3.975)
Alcohol	5 (2.6)	4 (2.6)	1 (2.8)	0.947 (cs=0.004)
Chronic disease	145 (75.9)	113 (72.9)	32 (88.9)	0.051 (cs=4,083)
Hypertension	73 (38.2)	55 (35.5)	18 (50.0)	0.106 (cs=2.607)
Diabetes	78 (40.8)	59 (38.1)	16 (52.8)	0.106 (cs=2.618)
Hyperlipidemia	31 (16.2)	24 (15.5)	7 (19.4)	0.562 (cs=0.337)
Heart failure	16 (8.4)	11 (7.1)	5 (13.9)	0.190 (cs=1.756)
Carotid stenosis	87 (45.5)	73 (47.1)	14 (38.9)	0.373 (cs=0.794)
Atrial fibrillation	32 (16.8)	20 (12.9)	12 (33.3)	0.003* (cs=8.743)
LA Diameter	35 (34-40)	35 (33-37)	43 (35.75-47)	<0.001* (z=-4,789)
LA Diameter High (LA >40 mm)	43 (22.5)	21 (13.5)	22 (61.1)	<0.001* (cs=37.885)
LAD Enlargement				
Normal	148 (77.5)	137 (86.2)	11 (34.4)	
Mild	21 (11)	11 (6.9)	10 (31.3)	<0.001* (cs=38.232)
Moderate	13 (6.8)	6 (3.8)	7 (21.9)	
Severe	9 (4.7)	5 (3.1)	4 (12.5)	
TOAST				
LAA	98 (51.3)	82 (52.9)	16 (44.4)	
Cardioembolic	54 (28.3)	35 (22.6)	19 (52.8)	0.002* (cs=16.634)
Small vessel	31 (16.2)	30 (19.4)	1 (2.8)	
Other etiologic cause	6 (3.1)	6 (3.9)	0	
Unknown cause	2 (1)	2 (1.3)	0	
Planned Treatment				
Antiaggregants	137 (71.7)	120 (77.4)	17 (47.2)	0.003* (cs=16.633)
Anticoagulant	50 (26.2)	31 (20)	19 (52.8)	
Combined	4 (2.1)	4 (2.6)	0	

LA: Left atrium, CVD: Cerebrovascular Disease, TOAST: Trial of Org 10172 in Acute Stroke Treatment, LAA: Large Artery Atherosclerosis
z: Mann Whitney U, cs: Chi-Square, * :This was statistically significant *p*<0.05

Echocardiography findings

The LAD was significantly larger in the recurrent stroke group than in the non-recurrent group (median [IQR]: 43 [35.75-47] mm vs. 35 [33-37] mm; $p<0.001$). Additionally, the proportion of patients with a high LAD (LAD >40 mm) was significantly higher in the recurrent stroke group (61.1% vs. 13.5%; $p<0.001$).

The severity of LAD also differed significantly between recurrent and non-recurrent cases. Recurrent patients had lower rates of normal LAD severity and higher rates of mild, moderate, and severe LAD severity ($p<0.001$).

Regarding the TOAST classification, recurrent stroke patients had a higher rate of CE and a lower rate of small vessel disease ($p=0.002$).

Anticoagulant use was more common in patients with recurrent ischemic stroke (52.8% vs. 20.0%; $p=0.003$).

Correlation analyses of echocardiography findings

Logistic regression analyses revealed that LAD, smoking, and AF were independently associated with recurrent ischemic stroke.

Model 1: When only LAD was evaluated, an increase in LAD was associated with a higher risk of recurrent stroke (O.R (Odds Ratio)=1.159, 95% CI for O.R=1.094-1.229, $p<0.001$).

Model 2: Including age and gender in the analysis, the effect of LAD on recurrent stroke risk remained significant, while age and gender did not show a significant effect.

Model 3: In this model, which included all variables, smoking (O.R=0.158, 95% CI for O.R=0.037-0.677, $p=0.013$), male gender (O.R =0.190, 95% CI for O.R=0.042-0.867, $p=0.032$), and carotid atherosclerosis (O.R=3.169, 95% CI for O.R=1.056-9.514, $p=0.040$) were found to be independently associated with recurrent ischemic stroke. LAD continued to significantly increase the risk of recurrent stroke in this comprehensive model (O.R=1.176, 95% CI for O.R=1.088-1.271, $p<0.001$).

Discussion

Our findings indicate that LAD, smoking, and AF are significantly associated with an increased risk of recurrent ischemic stroke. Age, HT, diabetes mellitus, and HL did not demonstrate a significant relationship with recurrent stroke. LAD was associated with CE and LAA subtypes. Additionally, logistic regression analyses revealed that male gender was associated with recurrent ischemic stroke.

We found that LAD was significantly larger in patients with recurrent ischemic stroke. This supports previous research suggesting that LA enlargement is associated with an increased risk of stroke due to AF and other cardiac pathologies [20-23]. Specifically, an increased LAD may lead to blood stasis and thrombus formation in the LA, thereby heightening the risk of cardioembolic events [24-26]. Logistic regression analyses in our study confirmed that an increase in LA diameter independently raised the risk of recurrent stroke. In terms of pathophysiology, left atrial enlargement leads to increased wall tension, which can interfere with normal electrical conduction and contribute to AF development. Additionally, dilation of the LA can cause contractile and endothelial dysfunction, which may predispose to thrombus formation. Left atrial enlargement may increase the risk of thrombosis through both mechanical and biochemical mechanisms, potentially leading to recurrent ischemic stroke. Therefore, managing left atrial dilation is crucial, particularly in patients with AF, to mitigate the risk of stroke. Several studies have highlighted the importance of LAD as a risk factor for recurrent stroke. For instance, LAD has been identified as a determinant risk factor in cryptogenic stroke [27, 28], though one study found it to be associated specifically with CE [29]. A meta-analysis of 66,007 participants and 3,549 stroke events established a significant association between LA index (LAI) and ischemic stroke, noting that each 1 cm increase in LAD was associated with a 24% increased likelihood of stroke [30]. Furthermore, another study indicated that increased LAI correlates with higher stroke incidence rates and mortality, suggesting that

LAI could be a valuable prognostic marker post-stroke [31]. In our study, LAD was found to be associated with CE stroke and LAA. However, no association was observed between LAD and stroke of unknown etiology. This lack of association may be attributed to the relatively small number of patients with ESUS. Our study also identified AF as an independent risk factor for recurrent ischemic stroke.

AF is a significant risk factor for ischemic stroke and is associated with a three- to five-fold increased risk [32]. AF increases the risk of CE stroke by promoting thrombus formation due to irregular heartbeats and blood stasis in the LA [33, 34]. AF is associated with a risk of CE stroke, high mortality, and morbidity, and it carries a relatively high rate of recurrence within the first 90 days [35]. Studies have demonstrated that early anticoagulant therapy following the diagnosis of AF reduces the risk of recurrent stroke [36, 37]. This supports the substantial role of AF in stroke recurrence. Consequently, anticoagulant therapy for patients with AF may be an effective strategy to reduce the risk of recurrent stroke. However, since AF is often paroxysmal, it may be missed during routine screenings in stroke patients. Therefore, structural changes in the LA should be considered. It should be noted that patients with left atrial dilation may have a higher risk of stroke and that left atrial dilation may support the presence of AF. Recurrent stroke diminishes patients' quality of life and increases mortality. Consequently, in patients with an increased LAD detected during routine echocardiographic evaluations, treatment adjustments should be considered with the possibility of underlying AF, even if AF is not directly detected. Another key finding of this study was that smoking significantly increased the risk of recurrent ischemic stroke, likely by accelerating vascular inflammation and atherosclerosis [38].

This finding is consistent with existing literature that underscores the detrimental effects of smoking on stroke recurrence. A study has found that continuing to smoke after the first stroke increases the risk of stroke recurrence and that there is a dose-response relationship with the amount of smoking [39]. In this study, the investigation focused solely on whether patients smoked or not, without considering the duration or amount of smoking. As a result, an analysis of the dose-response relationship could not be conducted. The elevated risk of recurrent stroke among smokers highlights the crucial need for smoking cessation programs to benefit stroke patients.

We evaluated other clinical and demographic factors, including age, gender, HT, diabetes mellitus, HL, and heart failure. Our logistic regression analyses revealed that male gender was associated with recurrent ischemic stroke. According to recent reports, no significant difference was found between men and women regarding the recurrence rate of ischemic stroke and the associated risk factors. These findings differ from the existing literature on the relationship between recurrent stroke and gender [40].

In conclusion, this study demonstrated that LAD, smoking, and AF may be independently associated with the risk of recurrent ischemic stroke. The impact of LAD on stroke risk should be considered an important parameter in the management of patients with atrial fibrillation. Smoking cessation programs and effective treatment of AF are critical for reducing the risk of recurrent stroke. Prospective, large-scale studies should aim to confirm and further elucidate these findings.

This study had a retrospective design, with data obtained from hospital records. As a result, there is a possibility that some data may be missing or inaccurate. Another limitation is the lack of data on the duration and amount of smoking. Another limitation of this study is the lack of detailed information on the types and dosages of medications used by the patients, due to the retrospective nature of the data. Additionally, the study was conducted at a single center, which may limit the generalizability of the results. The relatively small sample size further constrains the ability to extrapolate findings to a broader population. Therefore, the results should be interpreted with caution. Larger, multicenter, and prospective studies are needed to confirm these findings and to enhance their generalizability.

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Authors' contributions to the article: G.Z.D. conceptualized the study and developed the main hypothesis. S.B.A. designed the methodology. I.E.D. performed data analysis. Z.O. drafted the Discussion section. G.Z.D. reviewed, revised, and approved the final manuscript. All authors contributed to the study and approved the final version.

Conflict of interest: The authors declare that they have no conflict of interest to disclose.

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