

# Ischemic stroke in young adults: Risk factors, etiology, and outcome

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#### ABSTRACT

**Objectives:** This study aimed to determine the etiologies, risk factors, and poststroke functional status in young patients with ischemic stroke.

**Patients and methods:** The data of 89 patients (49 males, 40 females; mean age: 43.0±8.6 years; range, 20 to 55 years) diagnosed with ischemic stroke were retrospectively analyzed between January 2016 and May 2019.

**Results:** The majority of the patients (62.9%) were found to have modifiable risk factors before stroke, and these risk factors were associated with age and sex, but more than half of the patients (58.4%) had a stroke subtype of stroke of undetermined cause. Although early symptoms and long-term functional status of the subjects did not differ by stroke subtype, the subjects in this study had a milder course and better outcomes than the general population with stroke.

**Conclusion:** These results indicate the critical importance of accurate determination of risk factors and treating the underlying causes for the short- and long-term management of stroke in young adults.

Keywords: Prognosis, risk factors, stroke, young adult.

Stroke is the second most common cause of death worldwide after coronary artery disease (CAD).<sup>[1]</sup> Although it is considered a significant disease in the elderly population, stroke can also occur in the young age group, causing considerable morbidity and mortality. Compared to the elderly population, ischemic stroke is particularly significant in young individuals since it can cause severe disabilities during their most productive years. Globally, irrespective of ethnic group, sex, and age groups, hypertension (HT), diabetes mellitus (DM), smoking, alcohol consumption, diet, physical inactivity, cardiac causes, abdominal obesity, the apolipoprotein B/A1 ratio, and psychosocial factors are identified as potential modifiable risk factors for ischemic stroke.<sup>[2]</sup> Despite the well-defined risk factors, the accumulation of substantial data on primary prevention, and the increase in treatment options related to risk factors, the incidence of stroke has been reported to increase, particularly among young individuals, by 40% worldwide over the past decade.<sup>[3,4]</sup> However, although diagnostic methods and the options available for investigating the etiology of stroke have increased, the cause of a significant portion of young ischemic stroke cases remains unknown.[3] In light of this information, this study aimed to retrospectively examine young ischemic stroke patients admitted to our clinic, evaluating the accumulated data on risk factors, etiologies, and prognosis. Hence, we aimed to identify factors that may be related to the increasing rates of ischemic stroke despite the rise in diagnostic methods and investigations into etiology, thereby contributing to the literature on young ischemic stroke.

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## **PATIENTS AND METHODS**

Young patients who were admitted to the neurology clinic of the Necmettin Erbakan University Meram Faculty of Medicine with sudden onset focal or global cerebral function loss and diagnosed with ischemic stroke between January 2016 and May 2019 were retrospectively reviewed. Patients under the age of 18 or over the age of 55 and those with findings of intracranial hemorrhage, subarachnoid hemorrhage, or cerebral venous thrombosis on imaging were excluded from the study. A total of 152 cases were identified, but 63 cases were excluded from the study due to insufficient or unavailable diagnostic and treatment evaluations for stroke and missing initial visit examination and clinical follow-up information. Consequently, 89 patients (49 males, 40 females; mean age: 43.0±8.6 years; range, 20 to 55 years) were included in the study.

The patients' age, sex, initial examination findings, National Institute of Health Stroke Scale (NIHSS) scores at stroke onset, modified Rankin Scale (mRS) scores at stroke onset and at three months, and length of hospital stay were recorded. The functional dependency level of the patients was assessed according to the mRS as normal (0), mild (1-2), moderate (3), severe (4-5), and death (6). In the medical history of the patients, the presence of risk factors for stroke, namely DM, HT, atrial fibrillation (AF), CAD, heart failure (HF), dyslipidemia (DL), history of previous stroke, valvular heart disease (VHD), valve replacement (VR), history of cancer, peripheral artery disease (PAD), smoking, migraine, alcohol use, menstrual irregularities, early menopause, oral contraceptive (OC) use, and obstructive sleep apnea syndrome (OSAS), were investigated. Routine biochemistry, complete blood count, and serum autoantibody results were reviewed, and any results outside the reference values determined by the hospital laboratory were recorded as abnormal. In addition, the cardiac examinations, namely electrocardiography (ECG), 24- or 72-h rhythm Holter monitoring, transthoracic echocardiography (TTE), and transesophageal echocardiography (TEE), were also reviewed and recorded. Cranial magnetic resonance imaging (MRI) and computed tomography (CT), as well as angiographic imaging, were examined, and the presence of hemorrhage, ischemia and its stage, and the affected vascular areas were recorded. In light of the findings, the cases were classified according to their etiological types using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria, and the cases were divided into five groups based on their etiological

types. For patients who were on antiplatelet or anticoagulant therapy before the stroke, the duration of therapy and any discontinuation of therapy before the stroke were also recorded.

# Statistical analysis

The data were evaluated using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The suitability of the parameters to normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilks tests. In addition to descriptive statistical methods (mean, standard deviation, and frequency), Student's t-test was used for comparing normally distributed quantitative data that, whereas the Mann-Whitney U test was used for those that did not show normal distribution. For the comparison of qualitative data, the one-way chi-square test, chi-square test, Fisher exact chi-square test, Yates' correction for continuity, and Fisher-Freeman-Halton exact test were used. A p-value <0.05 was considered statistically significant.

#### RESULTS

No statistically significant difference was found between the distributions of male and female patients (p=0.340). The mean age of male patients was 44.2 $\pm$ 8.6 years, and the mean age of female patients was 41.4 $\pm$ 8.5 years, with no statistically significant difference between the two groups (p=0.127). Fourteen (15.7%) of the patients were between the ages of 20 and 34, 33 (37.1%) were between the ages of 35 and 44, and 42 (47.2%) were between the ages of 45 and 55. There was no statistically significant difference in the distribution of age groups between sexes (p=0.233, Figure 1).

It was found that 62.9% of the patients had at least one risk factor, and the most common risk factors were HT (32.6%), DM (19.1%), and CAD



Figure 1. Distribution of age groups among females and males.

(12.4%). The rates of CAD and myocardial infarction (MI) were higher in male patients, while there was no significant difference in the rates of other risk factors between sexes. The rate of DM (33.3%) was significantly higher in the 45 to 55 age group compared to the other age groups, while there was no significant difference in the rates of other risk factors according to age (Table 1).

In the evaluation of patients based on the number of risk factors, the rate of having two or more risk factors was significantly lower in the 20 to 34 age group compared to the 35 to 44 and 45 to 55 age groups (p=0.024 and p=0.06, respectively). There was no statistically significant difference in the number of risk factors between sexes (Table 2).

In the evaluation of patients according to the etiological subtypes of ischemic stroke, 14.6% had large artery atherosclerosis (LAA), 9% had cardioembolism (CE), 9% had small artery occlusion (SAO), 9% had stroke of other determined cause (SOC), and 58.4% had stroke of undetermined cause (SUC). In this study, among the cases with the CE stroke subtype (n=8), two had prosthetic valves, two had intracardiac thrombus, one had cardiomyopathy,

one had AF and mitral stenosis, one experienced MI within the last four weeks, and one had a patent foramen ovale. In the group with SOC (n=8), the most frequently identified cause was dissection (n=6, 75%), while other identified etiologies were vasculitis (n=1, 12.5%) and Sneddon syndrome (n=1, 12.5%). In the evaluation according to age groups, the LAA stroke subtype was more common in the 45 to 55 age group compared to the other age groups (p=0.054), while the SOC subtype was less common in the 45 to 55 age group compared to the other age groups. There was no significant difference in the rates of etiological subtypes between sexes (Table 3).

In the evaluation of risk factors according to the etiological subtypes of stroke, DM in the LAA group, MI and VR in the CE group, and DM and HT in the SAO group were statistically significantly more prevalent. In the SUC group, the rates of DM and HT were lower compared to the groups with a determined stroke etiology. In the evaluation based on the number of risk factors, the rate of the LAA stroke subtype was significantly higher and the rate of the SUC subtype was significantly lower in patients with two or more risk factors. The rate of the SAO stroke subtype was higher in patients

		Distr	ibutio	n of ris		ABLE 1 ors acc	ording to	sex a	nd age					
	To	otal	Fen	nales	Ma	ales	_	20-34	í years	35-44	í years	45-55	5 years	
Risk factors	n	%	n	%	n	%	Þ	n	%	n	%	n	%	Þ
Well-documented														
HT	29	32.6	11	27.5	18	36.7	0.48611	1	7.1	11	33.3	17	40.5	$0.070 \ddagger$
DM	17	19.1	6	15	11	22.4	0.53611	0	0	3	9.1	14	33.3	$0.004^{*}$
CAD	11	12.4	0	0	11	22.4	0.001*§	0	0	7	21.2	4	9.5	0.131§
MI	10	11.2	0	0	10	20.4	0.002*§	0	0	5	15.2	5	11.9	0.403§
Previous stroke	7	7.9	2	5	5	10.2	0.452§	0	0	3	9.1	4	9.5	0.753§
Dyslipidemia	5	5.6	0	0	5	10.2	0.062§	0	0	2	6.1	3	7.1	0.847§
Malignancy	4	4.5	3	7.5	1	2.0	0.322§	0	0	0	0	4	9.5	0.157§
AF	2	2.2	1	2.5	1	2	1.000§	0	0	1	3	1	2.4	1.000§
VR	2	2.2	2	5	0	0	0.199§	0	0	1	3	1	2.4	1.000§
HF	2	2.2	0	0	2	4.1	0.499§	0	0	1	3	1	2.4	1.000§
PAD	1	1.1	0	0	1	2	1.000§	0	0	1	3	0	0	0.528§
VHD	1	1.1	1	2.5	0	0	0.449	0	0	0	0	1	2.4	1.000§
Insufficiently documented														
Smoking	12	13.5	5	12.5	7	14.3	1.00011	2	14.3	4	12.1	6	14.3	1.000§
Alcohol use	3	3.4	0	0	3	6.1	0.249§	0	0	1	3	2	4.8	1.000§
Migraine	3	3.4	2	5	1	2	0.586§	1	7.1	2	6.1	0	0	0.176§
Menstrual irregularity†	3	7.5	3	7.5	-	-	-	0	0	3	20	0	0	0.055§
OC use†	3	7.5	3	7.5	-	-	-	1	11.1	2	13.3	0	0	0.320§
Early menopause†	1	2.5	1	2.5	-	-	-	0	0	0	0	1	6.3	1.000§
OSAS	1	1.1	0	0	1	2	1.000§	0	0	0	0	1	2.4	1.000§

HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; MI: Myocardial infarction; AF: Atrial fibrillation; VR: Valve replacement; HF: Heart failure; PAD: Peripheral artery disease; VHD: Valvular heart disease; OC: Oral contraceptive; OSAS: Obstructive sleep apnea syndrome; \* p<0.05; † Early menopause, menstrual irregularity, and OC use are specified for female patients; ‡ Chi-square test; § Fisher-Freeman-Halton exact test; || Yates' correction for continuity.

	Evaluation	of risk fa	TABLE 2 actors acco		ge and sex		
	No ris	k factor	Single r	isk factor	Two or mor		
	n	%	n	%	n	%	p
Age group (year)							0.018*
20-34	10	71.4	3	21.4	1	7.1	
35-44	12	36.4	5	15.2	16	48.5	
45-55	11	26.2	12	28.6	19	45.2	
Sex							0.2226
Female	15	37.5	12	30	13	32.5	
Male	18	36.7	8	16.3	23	46.9	

\* Chi-square test.

			Distr	ibution c	of etiolo		. <b>BLE 3</b> btypes a	ccordin	ig to age	and sex	X			
	To	otal	Fer	nale	М	ale		20-34	4 years	35-44	years	45-55	years	
	n	%	n	%	n	%	Þ	n	%	n	%	n	%	Þ
LAA	13	14.6	3	7.5	10	20.4	0.512	0	0	3	9.1	10	23.8	0.054
CE	8	9	4	10.0	4	8.2		2	14.3	3	9.1	3	7.1	0.697
SAO	8	9	3	7.5	5	10.2		0	0	1	3.0	7	16.7	0.074
SOC	8	9	4	10	4	8.2		4	28.6	4	12.1	0	0	0.001*
SUC	52	58.4	26	65	26	53.1		8	57.1	22	66.7	22	52.4	0.500

LAA: Large artery atherosclerosis; CE: Cardioembolism; SAO: Small artery occlusion; SOC: Stroke of other determined cause; SUC: Stroke of undetermined cause; Fisher-Freeman-Halton exact test; \* p < 0.05.

Evaluation o	τ. f etiological sι	<b>ABLE 4</b> ibtypes a	ccording t	o risk fac	tors		
	No risk factor Single risk factor Two or more risk factors						
	n	%	n	%	n	%	Þ
Large artery atherosclerosis	2	6.1	0	0	11	30.6	0.002*
Cardioembolism	1	3	2	10	5	13.9	0.319
Small artery occlusion	0	0	4	20	4	11.1	0.028*
Stroke of other determined cause	4	12.1	1	5	3	8.3	0.721
Stroke of undetermined cause	26	78.8	13	65	13	36.1	0.000*

Fisher-Freeman-Halton exact test; \* p<0.05.

with one risk factor compared to those with no risk factors (Table 4).

During the acute stroke attack, 68.5% of the patients had an mRS score  $\leq 2$ , and 67.4% had an NIHSS score  $\leq 4$ . When evaluated according to etiological subtypes, the proportion of cases with an NIHSS score  $\leq 4$  was 87.5% in the SOC group, 71.1% in the SUC group, 62.5% in the SAO group, 61.5% in the LAA group, and 37.5% in the CE group. No statistically significant difference was found in NIHSS scores during acute stroke according to different etiological subtypes. In the CE stroke subtype, the

proportion of cases with an NIHSS score  $\leq 4$  and mRS score  $\leq 2$  was 37.5%, which was lower compared to the other stroke subtypes; however, this difference was not statistically significant. The in-hospital mortality rate was 1.1%.

When the rates of investigations performed on the patients were evaluated, it was found that MRI was performed in 95.5% of patients, vascular examinations (magnetic resonance angiography, CT angiography, and digital subtraction angiography) in 100%, Holter ECG monitoring in 87.6%, TTE in 98.9%, TEE in 4.5%, coagulation

	Distribution		<b>TABLE 5</b> scores at tl	hree mor	nths (n=88	0			
	Norn	nal (0)	al (0) Milc		Moderate (3)		Severe (4-5)		
mRS		n	%	n	%	n	%	n	%
	20-34	12	85.7	2	14.3	0	0	0	0
Age (years)	35-44	23	69.7	7	21.2	2	6.1	1	3
	45-55	19	46.3	16	39.0	3	7.3	3	7.3
	Þ				0.1	77*			
	No risk factor	23	69.7	6	18.2	3	9.1	1	3.0
Number of risk	Single risk factor	11	55	7	35	1	5	1	5
	Two or more risk factors	20	57.1	12	34.3	1	2.9	2	5.7
	Þ				0.6	74*			
	LAA	9	69.2	2	15.4	0	0	2	15.4
	CE	3	37.5	4	50	1	12.5	0	0
Etiological subtype	SAO	3	37.5	4	50	1	12.5	0	0
	SOC	6	75	2	25	0	0	0	0
	SUC	33	64.7	13	25.5	3	5.9	3	5.9
	Þ				0.4	03‡			

mRS: Modified Rankin Scale; LAA: Large artery atherosclerosis; CE: Cardioembolism; SAO: Small artery occlusion; SOC: Stroke of other determined cause; SUC: Stroke of undetermined cause; \* Chi-square test; ‡ Fisher exact test.

tests in 83.1%, and serum autoantibody tests in 56.2%.

At three months, 89.8% of all cases were found to be functionally independent (mRS score  $\leq$ 2). No significant differences were found in the mRS scores at three months according to sex, age group, stroke subtype, number of risk factors, or affected vascular area (Table 5).

## DISCUSSION

Of the 89 cases included in the study, 40 (44.9%) were female, and 49 (55.1%) were male. Males were more frequently affected (65 to 67.7% for males, 32.5 to 35% for females) in many studies on young ischemic stroke patients; however, there are also some studies with no significant differences between sexes (51 to 55.4% for males, 44.6 to 49% for females).<sup>[5-8]</sup> In our study, while the number of male patients was higher, the difference in the number of male and female patients was not statistically significant.

The mean age of all patients was 42.97±8.59 years, the mean age of male patients was 44.22±8.55 years, and the mean age of female patients was 41.42±8.48 years. In the literature, the upper age limit defined for young ischemic stroke cases varies, and therefore, the mean ages reported in studies range from 36 to 46.9 years.<sup>[5,7-12]</sup> In the evaluation

according to age groups, approximately half of our patients (47.2%) were in the 45 to 55 age group, 37.1% were in the 35 to 44 age group, and 15.7% were in the 20 to 34 age group. The increase in the number of cases with increasing age is significant. There are studies in the literature reporting that approximately 60 to 70% of young ischemic stroke cases are in the 45 to 55 age range.<sup>[8,13]</sup> These studies indicate that risk factors such as HT, DM, DL, and smoking are more prevalent in patients aged 45 to 55 compared to those under the age of 45. These findings suggest that the higher prevalence of patients aged 45 and above in the young adult ischemic stroke group may be related to the higher prevalence of vascular risk factors in this age group.

When examined according to risk factors, the most common risk factors were HT (32.6%), DM (19.1%), and CAD (12.4%). In the literature, the most common risk factors reported were HT (35.9 to 52.9%), DL (45.5 to 71.8%), and smoking (34.7 to 48.7%).<sup>[8,14,15]</sup> However, the rates of DM (6.4 to 9.7%) and CAD (6 to 9%) in these studies were found to be lower compared to our study. In our study, DL was considered a risk factor only in patients with a known DL diagnosis at the time of admission. Additionally, due to the retrospective design of this study, the documentation of some modifiable risk factors, including smoking, was insufficient. The lower rates of DL and smoking

observed in our study are considered to be due these reasons. Among the insufficiently documented risk factors, smoking was present in 13.5% of cases, alcohol use in 3.4%, migraine in 3.4%, and OC use (females only) in 7.5%. In the literature, smoking is reported at rates between 9.5 and 55%, alcohol use between 9.5 and 33%, history of migraine between 4.9 and 26.5%, and OC use between 5.4 and 40%.<sup>[8,10,13,16,17]</sup> The discrepancies in the documentation or inquiry of these risk factors lead to variations in the reported rates across different studies. In our study, the insufficient documentation of these data is considered to have caused the low rates in these risk factors, and they may not reflect real-life rates. Therefore, inquiring about these risk factors in patients is crucial, particularly for primary prevention treatments.

In the evaluation of risk factors according to sex, the rates of CAD and MI were higher in male patients, while there was no significant difference in the rates of other risk factors between sexes. Studies indicate that DL, smoking, CAD, HT, DM, MI, and alcohol use are more frequently observed in male patients, while migraine is more common in female patients.<sup>[10,13,14]</sup> In the evaluation of risk factors according to age groups, the rate of DM (33.3%) in the 45 to 55 age group was statistically significantly higher compared to other age groups, whereas there was no significant difference in the rates of other risk factors according to age. In the literature, the rate of DM in the 45 to 55 age range (10.5 to 13.6%) is higher than in those under the age of 45 (5.6 to 7.6%).<sup>[13,16,18]</sup> Furthermore, there are studies indicating that HT, CAD, DL, AF, and PAD are also more prevalent in the 45 to 55 age group.<sup>[13,16,18]</sup>

There was no significant difference in the number of risk factors between sexes. In the evaluation of the number of risk factors according to age groups, the rate of having two or more risk factors was 7.1% in the 20 to 34 age group, 48.6% in the 35 to 44 age group, and 45.2% in the 45 to 55 age group, and the difference was statistically significant. In the literature, it is stated that the number of detected risk factors increases with age.[13] This suggests that conventional risk factors may be less prevalent in younger age groups and that other risk factors might become more prominent. Therefore, in young patients, it may be necessary to investigate and inquire about other risk factors (e.g., inflammation, active malignancy, genetic thrombophilia, and coagulopathy). In this study, 62.9% of the patients were found to have at least one risk factor. This rate is reported to be between 73 and 94.7% in the literature.<sup>[13,17]</sup> The reason for the lower proportion of cases with at least one risk factor in our study compared to other studies is considered to be related to the lower rates of smoking and DL in our patients, which are the most commonly identified risk factors in other studies. In the context of risk factors, the fact that approximately 90% of young ischemic stroke cases had modifiable risk factors suggests that stroke could be preventable in the majority of these cases. Therefore, it is considered necessary to conduct studies on raising awareness related to preventable risk factors in the young population, perform screenings for risk factors taking age groups into consideration, and develop the opinion that risk factor-based evaluations may again be needed in the follow-up of patient groups with planned treatments.

Although the frequency of etiological subtypes in young ischemic stroke patients varies in the literature, studies using the TOAST classification reported LAA in 5 to 21%, CE in 9 to 20%, SAO in 7 to 18%, SOC in 8 to 26%, and SUC in 15 to 57%.[8,10,16,19,20] Our results were similar to the literature data; however, the proportion of cases with SUC was higher in our study. In a multicenter study, it was noted that if low-risk CE cases and cases with weaker causal relationships to stroke, such as coagulopathies, which were included in the SOC group, were considered to be SUC, the proportion of undetermined cases would increase from 40 to 60%.<sup>[21]</sup> In our study, all stroke cases with uncertain etiologies were included in the SUC group during etiological classification.

In the assessment of the distribution of etiological subtypes by sex, no significant difference was found between female and male patients. The rates of etiological subtypes vary by sex in previous studies. There are studies indicating that LAA and SAO are more common in males, while CE, SAO, and SOC are more frequently identified in females.[8,10,16] The higher prevalence of LAA and SAO subtypes in males is suggested to be related to the higher rates of vascular risk factors, such as HT, DL, and smoking. In our study, the lack of a difference in the distribution of etiological subtypes according to sex could be related to the fact that despite the higher rates of CAD and MI observed in males, no significant differences were found in other vascular risk factors between sexes.

When the distribution of etiological subtypes was evaluated according to age groups, the LAA stroke subtype was higher in the 45 to 55 age group compared to the other age groups (p=0.054), whereas the SOC subtype was significantly lower

in the 45 to 55 age group compared to the other age groups. In the literature, there are studies that reported higher rates of LAA and SAO in patients aged 45 and older and higher rates of SOC in patients under the age of 45.[8,16] The increase in vascular risk factors, particularly the burden of atherosclerosis, with age is considered to be associated with the higher rates of LAA and SAO. In our study, no significant increase was found in the frequency of vascular risk factors other than DM in patients over the age of 45. Therefore, the inability to reach statistical significance in the rates of LAA and SAO stroke subtypes in this age group in our study could be related to this finding. Another point worth emphasizing is that the different age limits used in studies with age-related etiological evaluations in the literature may be related to the differences in results.

In the evaluation of risk factors according to the etiological subtypes of stroke, the rates of DM in the LAA group, MI and VR in the CE group, and DM and HT in the SAO group were statistically significantly higher, whereas in the SUC group, the rates of DM and HT were lower compared to the groups with a determined stroke etiology. Although there are few studies in the literature examining the distribution of risk factors according to etiological subtypes, our findings are similar.<sup>[12,22]</sup> In our study, the rates of LAA and SAO stroke subtypes increased with the number of risk factors. A study evaluating the number of risk factors according to etiological subtypes reported that the proportion of cases with risk factors was higher in the LAA and SAO groups, whereas the proportion of cases without risk factors was higher in the SOC group.<sup>[23]</sup> The increase in the rates of LAA and SAO stroke subtypes with the number of modifiable risk factors is considered to be related to the fact that vascular risk factors such as HT, DM, and DL, which impact the atherosclerotic process, constitute the majority of these risk factors. This suggests that in cases with a high number of risk factors at the time of admission, LAA and SAO stroke subtypes should be considered primarily, and the diagnostic and treatment strategies should be arranged accordingly.

In our study, 68.5% of the patients had an mRS score  $\leq 2$ , and 67.4% had an NIHSS score  $\leq 4$  during the acute stroke attack. In other studies, the mean NIHSS scores during acute stroke attacks ranged between 3.1 and 4.3.<sup>[9,12,17,24]</sup> Our findings are similar to the results reported in these studies, supporting the notion that stroke in young adults is mostly mild in severity. Although no statistically

significant difference was found in NIHSS scores during acute stroke among the different etiological subtypes, the findings suggest that stroke severity was higher in the CE subtype compared to other groups. This highlights the need for meticulous treatment planning and clinical follow-up in young patients with cardiogenic risk factors, considering the potentially devastating outcomes of ischemic stroke in these patients.

In the literature, studies on prognosis exhibit varying follow-up durations, with some studies following cases for up to approximately 11 years. These studies reported 80 to 90% of the cases to be functionally independent (mRS score  $\leq 2$ ) after a stroke, [6,9,11,17,25] and it was indicated that being over 35 years old and the female sex negatively affected functional outcomes.[25,26] In the evaluation of functional outcomes of the patients (n=88) at the three-month follow-up in our study, 100% of the patients in the 20 to 34 age group, 90.9% of the patients in the 35 to 44 age group, 85.3% of the patients in the 45 to 55 age group, and 89.8% of all patients were functionally independent (mRS score  $\leq 2$ ). Although the obtained rates indicated that the rate of functional independence decreased with advancing age, no statistically significant difference was found in the three-month mRS scores between sexes and age groups. Previous studies reported higher mortality rates in the LAA and CE stroke subtypes;<sup>[27,28]</sup> however, there are no reported differences in functional outcomes between etiological subtypes.<sup>[6,17,28]</sup> In our study, 100% of the cases in the SOC group, 90.2% in the SUC group, 87.5% in the CE stroke subtype, 87.5% in the SAO stroke subtype, and 84.6% in the LAA stroke subtype had mRS scores  $\leq 2$  at three months, with no statistically significant differences in mRS scores between the groups. In the CE stroke subtype, the more than twofold increase in the rate of patients with an mRS score ≤2 from 37.5% at stroke onset to 87.5% at the three-month follow-up was noteworthy. Another noteworthy point was that such a proportional change was not observed in other stroke subtypes except for the CE subtype. Additionally, no significant relationship was found between the number of risk factors the patients had and their three-month mRS scores. This finding is consistent with the literature.[23]

The limitations of our study included the retrospective design, which led to incomplete documentation of risk factors (e.g., smoking, alcohol use, OC use, and migraine), resulting in some risk factors not reflecting their true values. In addition, the small number of patients limited the number of patients in some etiological subgroups.

In conclusion, considering our findings with those in the literature, the risk factors and stroke etiologies in the young adult ischemic stroke group differ from those in the elderly population. In young individuals, although the likelihood of identifying multiple potential causes is higher, the etiological cause remains undetermined in the majority of young stroke patients. Furthermore, considering the long-term consequences of stroke and the burden it imposes on patients, their families, and society, the importance of acute phase management and primary/secondary prevention treatments in young stroke patients increases. Therefore, there is a need for the development of guidelines for the management of stroke in young patients and for diagnostic and treatment strategies to be determined based on recent data. The data obtained from studies conducted on young ischemic stroke patient groups are crucial for the development of these strategies. For all these reasons, there is still a need for multicenter prospective studies with standardized inclusion and follow-up criteria investigating the etiology, clinical course, and functional outcomes in young ischemic stroke patients.

**Ethics Committee Approval:** The study protocol was approved by the Necmettin Erbakan University Meram Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee (date: 05.07.2019, no: 91). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

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

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# REFERENCES

 Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: The GBD 2013 study. Neuroepidemiology 2015;45:161-76. doi: 10.1159/000441085.

- O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet 2010;376:112-23. doi: 10.1016/S0140-6736(10)60834-3.
- Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med 2016;45:e391-8. doi: 10.1016/j.lpm.2016.10.003.
- Griffiths D, Sturm J. Epidemiology and etiology of young stroke. Stroke Res Treat 2011;2011:209370. doi: 10.4061/2011/209370.
- Varona JF, Guerra JM, Bermejo F, Molina JA, Gomez de la Cámara A. Causes of ischemic stroke in young adults, and evolution of the etiological diagnosis over the long term. Eur Neurol 2007;57:212-8. doi: 10.1159/000099161.
- Leys D, Bandu L, Hénon H, Lucas C, Mounier-Vehier F, Rondepierre P, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. Neurology 2002;59:26-33. doi: 10.1212/wnl.59.1.26.
- Ji R, Schwamm LH, Pervez MA, Singhal AB. Ischemic stroke and transient ischemic attack in young adults: Risk factors, diagnostic yield, neuroimaging, and thrombolysis. JAMA Neurol 2013;70:51-7. doi: 10.1001/ jamaneurol.2013.575.
- Schneider S, Kornejeva A, Vibo R, Kõrv J. Risk factors and etiology of young ischemic stroke patients in Estonia. Stroke Res Treat 2017;2017:8075697. doi: 10.1155/2017/8075697.
- Özer İ, Sorgun M, Rzayev S, Kuzu M, Tezcan S, Yılmaz V, et al. Etiologic subtypes, risk factors and outcome of acute ischemic stroke with young patients. Turk J Neurol 2015;21:159-64. doi: 10.4274/tnd.68725.
- Dash D, Bhashin A, Pandit AK, Tripathi M, Bhatia R, Prasad K, et al. Risk factors and etiologies of ischemic strokes in young patients: A tertiary hospital study in north India. J Stroke 2014;16:173-7. doi: 10.5853/jos.2014.16.3.173.
- 11. Putaala J. Ischemic stroke in young adults (Doctoral Thesis). Helsinki: University of Helsinki; 2010.
- Akıncı Y. Genç İskemik inme hastalarında inme lokalizasyonu ile inme etiyolojisi arasındaki ilişki [Specialization Thesis]. İstanbul: İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi; 2019.
- 13. von Sarnowski B, Putaala J, Grittner U, Gaertner B, Schminke U, Curtze S, et al. Lifestyle risk factors for ischemic stroke and transient ischemic attack in young adults in the Stroke in Young Fabry Patients study. Stroke 2013;44:119-25. doi: 10.1161/STROKEAHA.112.665190.
- 14. Putaala J, Yesilot N, Waje-Andreassen U, Pitkäniemi J, Vassilopoulou S, Nardi K, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: The 15 cities young stroke study. Stroke 2012;43:2624-30. doi: 10.1161/STROKEAHA.112.662866.
- 15. Crespo Pimentel B, Willeit J, Töll T, Kiechl S, Pinho E Melo T, Canhão P, et al. Etiologic evaluation of ischemic stroke in young adults: A comparative study between two European centers. J Stroke Cerebrovasc Dis 2019;28:1261-6. doi: 10.1016/j.jstrokecerebrovasd is.2019.01.019.

- 16. Putaala J, Metso AJ, Metso TM, Konkola N, Kraemer Y, Haapaniemi E, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: The Helsinki young stroke registry. Stroke 2009;40:1195-203. doi: 10.1161/STROKEAHA.108.529883.
- Goeggel Simonetti B, Mono ML, Huynh-Do U, Michel P, Odier C, Sztajzel R, et al. Risk factors, aetiology and outcome of ischaemic stroke in young adults: The Swiss Young Stroke Study (SYSS). J Neurol 2015;262:2025-32. doi: 10.1007/s00415-015-7805-5.
- Kivioja R, Pietilä A, Martinez-Majander N, Gordin D, Havulinna AS, Salomaa V, et al. Risk factors for earlyonset ischemic stroke: A case-control study. J Am Heart Assoc 2018;7:e009774. doi: 10.1161/JAHA.118.009774.
- Kwon SU, Kim JS, Lee JH, Lee MC. Ischemic stroke in Korean young adults. Acta Neurol Scand 2000;101:19-24. doi: 10.1034/j.1600-0404.2000.00004.x.
- 20. Kes VB, Zavoreo I, Demarin V. Etiology and diagnostic work-up in young stroke patients. Period Biol 2012;114:355-9.
- Yesilot Barlas N, Putaala J, Waje-Andreassen U, Vassilopoulou S, Nardi K, Odier C, et al. Etiology of firstever ischaemic stroke in European young adults: The 15 cities young stroke study. Eur J Neurol 2013;20:1431-9. doi: 10.1111/ene.12228.
- 22. Cerrato P, Grasso M, Imperiale D, Priano L, Baima C, Giraudo M, et al. Stroke in young patients: Etiopathogenesis and risk factors in different age classes. Cerebrovasc Dis 2004;18:154-9. doi: 10.1159/000079735.

- 23. Putaala J, Haapaniemi E, Kaste M, Tatlisumak T. How does number of risk factors affect prognosis in young patients with ischemic stroke? Stroke 2012;43:356-61. doi: 10.1161/STROKEAHA.111.635276.
- Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, et al. Ischaemic stroke in young adults: Predictors of outcome and recurrence. J Neurol Neurosurg Psychiatry 2005;76:191-5. doi: 10.1136/ jnnp.2004.040543.
- 25. Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. J Neurol 2004;251:1507-14. doi: 10.1007/ s00415-004-0583-0.
- 26. Synhaeve NE, Arntz RM, van Alebeek ME, van Pamelen J, Maaijwee NA, Rutten-Jacobs LC, et al. Women have a poorer very long-term functional outcome after stroke among adults aged 18-50 years: The FUTURE study. J Neurol 2016;263:1099-105. doi: 10.1007/s00415-016-8042-2.
- 27. Putaala J. Ischemic stroke in young adults. Continuum (Minneap Minn) 2020;26:386-414. doi: 10.1212/ CON.00000000000833.
- 28. Kappelle LJ, Adams HP Jr, Heffner ML, Torner JC, Gomez F, Biller J. Prognosis of young adults with ischemic stroke. A long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults. Stroke 1994;25:1360-5. doi: 10.1161/01.str.25.7.1360.