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Impact of Gender on Risk Factors and Stroke Etiology in Young Ischemic Stroke Patients: A Retrospective Observational Study

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ABSTRACT

Introduction: The lack of clarity regarding the upper age limit for defining ischemic stroke in young individuals, and the absence of a gender-based distinction, make it difficult to determine the true incidence of stroke in young people and to standardize the approach to elucidating its etiology. This study aimed to examine the risk factors and etiology of ischemic stroke in young individuals, as well as to evaluate their distribution by gender.

Methods: This retrospective, observational, single-center study evaluated stroke risk factors and etiologies in 200 patients aged 18–55 diagnosed with ischemic stroke, and their distribution among male and female patients.

Results: The mean age was higher in males, who accounted for 58.5% of the patients. Smoking, alcohol use, and coronary artery disease (CAD) were more common in men, while anemia, migraine, and oral contraceptive use were more common in women. The most common etiological subgroup was stroke of other determined etiology (SODE) which was more common in women. Small vessel occlusion (SVO) was more common in men. In women, the mean ages of etiological subgroups were similar, but in men, the large artery atherosclerosis (LAA) group had a significantly higher mean age than the stroke of undetermined etiology and SODE groups.

Conclusion: Risk factors and etiology showed significant differences by gender. The proportion of etiological subgroups is consistent with earlier studies where the upper age limit was lower, suggesting that 55 years of age may be an appropriate upper age limit for young stroke. However, the finding that SVO and CAD, in which classical vascular risk factors play a major role, were more frequent in men, and that the mean age of men with LAA was older than that of men in other subgroups, indicates that the upper age limit for young stroke should most likely be lower in men.

Keywords: Cerebrovascular diseases, ischemic stroke, stroke etiology, stroke in young adults, stroke risk factor

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INTRODUCTION

Stroke, fundamentally regarded as a disease of the elderly population, also occurs in young patients, although less frequently, and ranks fifth among causes of death in individuals aged 15–59 (1). The term "young stroke" has been used to describe cases occurring at ages where stroke is not expected because of the absence of traditional cardiovascular risk factors. The use of this term has aimed to enhance the understanding of stroke risk factors and etiology in young individuals, thereby enabling the development of appropriate strategies for diagnosis and treatment. However, until today, there has been no consensus on what the upper age limit should be to define these cases. In the literature, the upper age limit shows wide variation, ranging between 30 and 59 years, and unlike in diseases such as premature coronary artery disease (CAD), where similar risk factors are observed, it has not been stratified according to the physiological differences between men and women (2,3). Studies conducted in different populations, using different upper age cutoffs, have reported that ischemic stroke is the most common type of stroke across all age groups, as observed in general (4). In young patients with ischemic stroke, common etiologies observed in elderly patients such as large-artery atherosclerosis and atrial fibrillation (AF) are replaced by rare genetic and hereditary causes of stroke. This necessitates that physicians consider a wide range of possible etiologies in the differential diagnosis and often perform numerous laboratory and imaging tests. Unfortunately, despite advances in imaging, hematological, and genetic testing methods,

Highlights

- **Young adult ischemic stroke shows clear sex-specific patterns.**
- **Men more often have traditional atherosclerotic risk factors and etiologies.**
- **The leading cause of ischemic stroke was dissections in women.**
- **The leading CE source was septal defects in women and LVD in men.**
- **55 years can be used as a practical cutoff with a slightly younger threshold for men.**

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the etiology of stroke cannot be determined in a significant proportion of patients (16–40%) (2,4). Since many women enter menopause between the ages of 45–55, and the prevalence of atherosclerotic diseases is lower in premenopausal women, we defined the upper age limit of 55 years for this study. Accordingly, we investigated the risk factors and causes of ischemic stroke observed in young patients, as well as their distribution between male and female patients (5).

METHODS

Study Setting and Study Design

This retrospective, observational, and single-center study was performed between April 1, 2019, and September 1, 2019, at Istanbul University – Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Neurology Department. It is a tertiary university hospital in the city center of Istanbul, Türkiye's most populous city. Istanbul University – Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Clinical Research Ethics Committee approval was obtained (Date: March 5, 2019, Decision No: 83045809-604.01.02).

Participant Selection and Measurements

Within the scope of the study, the medical records of ischemic stroke patients admitted between January 2000 and March 2019 were retrospectively reviewed. The inclusion criteria were as follows: to be 18–55 years of age, to be present with symptoms and signs of sudden-onset focal or global cerebral dysfunction, and to be diagnosed with ischemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The exclusion criteria were as follows: to be diagnosed with transient ischemic attack, to have ischemic stroke associated with severe head trauma or asphyxia, to have ischemic stroke secondary to angiographic procedures, or to be diagnosed with cerebral venous sinus thrombosis. A total of 200 patients who met the study criteria were identified.

The age, gender, body mass index (BMI) categories, past medical history, and family history of stroke of the patients were examined. Past medical history included diabetes mellitus (DM), hypertension (HTN), AF, heart failure, valve replacement, CAD, history of coronary bypass or stenting, myocardial infarction (MI), hyperlipidemia (HLD), peripheral arterial disease, sleep-related breathing disorders (SRBDs), migraine, alcohol-tobacco-illicit drug use, previous stroke, and other conditions. In female patients, the use of oral contraceptive (OCP) was also assessed. Patients who smoked at least half a pack/day (10 cigarettes/day) for more than 6 months prior to stroke onset were classified as smokers; patients who consumed at least one drink/day of alcohol for more than 6 months were considered alcohol users. For oral contraceptive use, regular use for at least 3 months prior to stroke onset was required.

The available results of head CT, MRI brain, carotid-vertebral doppler ultrasonography, magnetic resonance angiography (MRA) and/or computed tomography angiography (CTA) of head and neck, digital subtraction angiography (DSA), electrocardiogram, transthoracic and transesophageal echocardiogram, transcranial doppler, ambulatory rhythm monitoring, complete blood count, erythrocyte sedimentation rate, routine biochemistry, toxicology, glycated hemoglobin, lipid profile, thyroid function tests, prothrombin time, activated partial thromboplastin time, international normalized ratio, peripheral smear, syphilis tests, human immunodeficiency virus (HIV) tests, rheumatoid factor, antinuclear antibody, anti-double-stranded deoxyribonucleic acid antibodies, complement component 3 and 4, anticardiolipin antibodies, antiphospholipid antibodies, anti-neutrophil cytoplasmic antibodies, fibrinogen, D-dimer, protein C, protein S, antithrombin III, lupus anticoagulant (LA), factor V Leiden mutation, prothrombin gene mutation, methylenetetrahydrofolate reductase (MTHFR) gene mutation, plasminogen activator inhibitor mutation, α-galactosidase A gene mutation, and NOTCH3 gene mutation were examined. Based on the available data, patients were categorized into 5 groups according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system, which is the most widely used system in clinical studies to categorize stroke etiology: large-artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), stroke of other determined etiology (SODE), and stroke of undetermined etiology (SUE) (6). Ischemic stroke risk factors and stroke etiologies in patients were classified and their distribution by gender was examined.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) for Windows version 25.0 program was used for statistical analysis of the findings obtained as a result of the study. While presenting descriptive analyses, mean, standard deviation (SD), median, and minimum-maximum values were used. The normality of distribution of variables was assessed using histogram techniques and the Kolmogorov-Smirnov test. Pearson's Chi-Square test and Fisher's Exact test were used for the evaluation of contingency tables (2×2). Non-parametric variables that did not follow a normal distribution were analyzed between two groups using the Mann-Whitney U test, and among more than two groups using the Kruskal-Wallis test. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic Findings

A hundred and seventeen of the patients were male (58.5%) and 83 (41.5%) were female. The mean age at stroke onset was 43.4 (±9.5) years. The mean age at stroke onset was higher in male patients compared to female patients (44.3±9.9 vs. 42.2±8.8, p=0.021).

Risk Factors

Hyperlipidemia (HLD) was the most common modifiable risk factor observed in 49% of patients (n=98). This was followed by smoking (n=91, 45.5%) and HTN (n=75, 37.5%), respectively. These three modifiable risk factors were followed by anemia in 26% (n=52) of patients, DM in 25% (n=50), and obesity in 23.5% (n=47). A positive family history of stroke, present in 22.5% (n=45), was the most common non-modifiable risk factor. These risk factors were followed by alcohol use (15%, n=30), previous history of stroke (n=28, 14%), and CAD (n=27, 13.5%). MTHFR gene mutations were the most frequently observed genetic risk factor associated with stroke (n=27, 13.5%).

A total of 21 patients (13.5%) reported symptoms of obstructive sleep apnea (OSA) at a severity that affected daily activities prior to stroke (defined as ≥2 of the following: witnessed apnea, loud snoring, awakening with choking or gasping, non-restorative sleep, excessive daytime sleepiness, fatigue, or insomnia). None of these patients had undergone formal sleep testing prior to stroke; instead, they reported these symptoms during post-stroke risk factor evaluation. Since post-stroke formal sleep study results were not included in the study, SRBDs were not classified as a risk factor; however, it was deemed noteworthy to mention due to the high frequency of reported symptoms.

When stroke risk factors were analyzed by sex, the most common risk factors in men were smoking, HLD, and HTN, whereas in women they were HLD, HTN, and anemia. Smoking, alcohol use, and CAD were statistically significantly higher in men than in women. In female patients, anemia, migraine, and OCP use as stroke risk factors were statistically significantly more common. Risk factors in patients and distribution of these risk factors by gender are given in Table 1.

Stroke Etiology

According to the TOAST classification, etiological subgroups of the cases were SODE in 35.5% (n=71), CE in 21% (n=42), LAA in 15.5% (n=31), SVO in 14.5% (n=29), and SUE in 13.5% (n=27) of the patients. When the mean age of the etiological groups was examined, it was seen that the mean age of the LAA group was statistically significantly higher compared to the CE, SODE, and SUE groups. Mean age of the patients according to etiological groups are shown in Table 2.

The incidence rates of etiological groups in women and men were examined. The most common etiological subgroup in both genders was SODE, followed by CE. Among men, LAA, SVO, and SUE followed in descending order, while among women, the sequence was SUE, LAA, and SVO. Stroke of other determined etiology was significantly more common among women, whereas SVO was significantly more common among men (p=0.004 and p=0.4, respectively). The mean age of men with LAA was significantly higher than that of men with SODE and SUE. There was no significant difference between the mean ages of male and female patients in the etiological subgroups (see Table 2).

Among patients with SODE, 41 (56.75%) had non-atherosclerotic, non-inflammatory causes; 18 (25.35%) had hematological disorders and coagulopathies; 11 (15.49%) had inflammatory causes; and 1 had malignancy-related stroke. In 41 cases with non-atherosclerotic non-inflammatory causes, the most common cause of stroke was dissections (n=31, 75.6%) and constituted the most common etiological subgroup of SODE in both genders. Additionally, dissections were the most common cause of stroke in female patients. Of the dissection cases, 16 (51.6%) were in the carotid arteries and 15 (48.4%) were in the vertebral arteries. Carotid dissections were more frequent among women (n=10, 58.82%), whereas vertebral artery dissections were more frequent among men (n=8, 57.14%), though the difference was not statistically significant. The second most common subgroup of SODE was stroke due to hematological disorders and coagulopathies, with LA positivity being the most frequent cause (n=6, 33.3%). The incidence of stroke because of hematological disorders and coagulopathies was higher in women compared to males (p=0.02). The most common etiology detected in the inflammatory disease-associated stroke group was isolated central nervous system vasculitis.

Table 1. The prevalence of ischemic stroke risk factors in patients and their distribution by gender

Risk factor	All cases (n=200)	Female (n=83)	Male (n=117)	p value*
Hyperlipidemia	98 (49%)	38 (45.8%)	60 (51.3%)	0.43
Smoking	91 (45.5%)	27 (32.5%)	64 (54.7%)	0.002
Hypertension	75 (37.5%)	30 (36.1%)	45 (38.5%)	0.739
Anemia	52 (26%)	30 (36.1%)	22 (18.8%)	0.006
Diabetes mellitus	50 (25%)	15 (18.1%)	35 (29.9%)	0.057
Obesity	47 (23.5%)	24 (28.9%)	23 (19.7%)	0.128
Positive family history for stroke	45 (22.5%)	19 (22.9%)	26 (22.2%)	0.911
Alcohol use	30 (15%)	4 (4.8%)	26 (22.2%)	0.001
History of prior stroke	28 (14%)	9 (10.8%)	17 (14.4%)	0.52
Coronary artery disease	27 (13.5%)	5 (6.02%)	22 (18.8%)	0.009
MTHFR gene mutations (C677T and A1298C)	27 (13.5%)	10 (12.1%)	17 (14.5%)	0.613
Migraine	20 (10%)	15 (18.1%)	5 (4.3%)	0.001
Hyperhomocysteinemia	13 (6.5%)	4 (4.8%)	9 (7.7%)	0.56
Thrombocytosis	9 (4.5%)	3 (3.6%)	6 (5.1%)	0.74
Heart failure	8 (4)	4 (4.8%)	4 (3.4%)	0.72
Factor V Leiden mutation	7 (3.5%)	2 (2.4%)	5 (4.3%)	0.7
PAI mutation	7 (3.5%)	4 (4.8%)	3 (2.6%)	0.45
Prothrombin gene mutation	6 (3%)	3 (3.6%)	3 (2.6%)	0.69
Chronic kidney disease	4 (2%)	2 (2.4%)	2 (1.7%)	1
AIDS	2 (1%)	0 (0%)	2 (1.7%)	0.5
Polycythemia	2 (1%)	0 (0%)	2 (1.7%)	0.5
Oral contraceptive use	7 (3.5%)	7 (8.4%)	0 (0%)	0.018

AIDS: acquired immunodeficiency syndrome; MTHFR: methylenetetrahydrofolate reductase; PAI: plasminogen activator inhibitor; *: p <0.05.

Table 2. Mean age of the patients according to etiological groups

TOAST Classification	All cases	Female	Male
Large artery atherosclerosis	50.8 (±2.7)	48.5 (±5.5)	51.6 (±2.6)
Cardioembolism	43.6 (±11.1)	41.1 (±11.2)	45.1 (±10.9)
Small vessel occlusion	45.5 (±8.6)	44.57 (±9.7)	45.7 (±8.4)
Stroke of other determined etiology	40.2 (±8.7)	40.6 (±8)	39.8 (±9.6)
Stroke of undetermined etiology	41.1 (±9.7)	43.07 (±7.9)	39.4 (±10.9)
p value*	<0.00001	0.17	0.000039

*: p <0.05.

In the CE group, the most common etiology was atrial septal defects (11 patent foramen ovale [PFO], 3 atrial septal aneurysm cases; n=14, 33.3% of all CE cases), followed by left ventricular dysfunction (LVD). Left ventricular dysfunction was the most common cause of CE in men and was statistically significantly higher in male patients than female patients (n=12 vs n=1, p=0.02). In women, the most common cardioembolic etiology was PFO.

In the SUE group, 5 patients (18.5%) underwent a full diagnostic workup with no identifiable etiology, and the remaining 22 patients (81.5%) were inadequately investigated. All inadequately investigated patients had discontinued follow-up; thus, their evaluations could not be completed. Subgroups of ischemic stroke according to TOAST classifications are given in Table 3.

Table 3. Subgroups of ischemic stroke according to TOAST classification and their distribution by gender

TOAST Classification	All cases (n=200)	Female (n=83)	Male (n=117)	p value*
STROKE of OTHER DETERMINED ETIOLOGY	71 (35.5)	39 (46.9%)	32 (27.4%)	0.004
Non-atherosclerotic non-inflammatory causes	41 (56.8%)	20 (24.1%)	21 (17.9%)	2.69
Dissection	31 (15.5%)	17 (20.5%)	14 (11.9%)	0.14
CADASIL	3 (1.5%)	1 (1.2%)	2 (1.7%)	0.77
Moyamoya disease	2 (1%)	1 (1.2%)	1 (0.9%)	1
Susac syndrome	1 (0.5%)	1 (1.2%)	0	0.42
Sneddon syndrome	1 (0.5%)	1 (1.2%)	0	0.42
Fabry disease	1 (0.5%)	0	1 (0.9%)	1
Marfan syndrome	1 (0.5%)	0	1 (0.9%)	1
Aneurysm	1 (0.5%)	0	1 (0.9%)	1
Hematological disorders and hypercoagulable states	18 (25.4%)	12 (14.5%)	6 (5.1%)	0.02
Lupus anticoagulant	6 (3%)	3 (3.6%)	3 (2.6%)	0.69
Protein S deficiency	5 (2.5%)	4 (4.8%)	1 (0.9%)	0.16
Protein C deficiency	2 (1%)	2 (2.4%)	0	0.17
Anti-fosfolipid syndrome	2 (1%)	1 (1.2%)	1 (0.9%)	1
Factor V Leiden mutation	1 (0.5%)	1 (1.2%)	0	0.42
Homozygous PAI mutation	1 (0.5%)	1 (1.2%)	0	0.42
Hypofibrinogenemia	1 (0.5%)	0	1 (0.9%)	1
Infectious or inflammatory diseases	11 (15.5%)	5 (6%)	6 (5.1%)	0.07
Central nervous system vasculitis	6	3 (3.1%)	3 (2.6%)	0.69
Takayasu arteritis	2(1%)	1 (1.2%)	1 (0.9%)	1
AIDS	2(1%)	0	2 (1.7%)	0.5
Leukocytoclastic vasculitis	1	1 (1.2%)	0	0.42
Cancer-related	1 (0.5%)	1 (1.2%)	0	0.42
CARDIOEMBOLISM	42 (21%)	16 (19.3%)	26 (22.2%)	0.614
Patent foramen ovale	11 (5.5%)	7 (8.4%)	4 (3.4%)	0.21
Hypokinetic or akinetic left ventricular segment	13 (6.5%)	1 (1.2%)	12 (10.3%)	0.02
Atrial fibrillation	5 (2.5%)	2 (2.4%)	3 (2.6%)	1
Atrial septal aneurysm	3 (1.5%)	0	3 (2.6%)	0.27
Congestive heart failure	2 (1%)	1 (1.2%)	1 (0.9%)	1
Mitral valve prolapse	2 (1%)	1 (1.2%)	1 (0.9%)	1
Mechanical prosthetic valve	2 (1%)	2 (2.4%)	0	0.17
Left ventricular thrombus	2 (1%)	0	2 (1.7%)	0.5
Recent myocardial infarction	1 (0.5%)	1 (1.2%)	0	0.42
Atrial myxoma	1 (0.5%)	1 (1.2%)	0	0.42
LARGE ARTERY ATHEROSCLEROSIS	31 (15.5%)	8 (9.6%)	23 (19.7%)	0.054
SMALL VESSEL OCCLUSION	29 (14.5%)	7 (8.4%)	22 (18.8)	0.04
STROKE of UNDETERMINED ETIOLOGY	27 (13.5%)	13 (15.7%)	14 (11.9%)	0.451

AIDS: acquired immunodeficiency syndrome; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PAI: plaminogen activator inhibitor; *: p <0.05.

DISCUSSION

Young stroke is more common in men than in women, however, under the age of 35 it has been reported to occur more frequently in women due to delivery and OCP use (7–8). In our study examining patients presenting within a specific time frame, the majority of cases were male, and this pattern did not change in cases under 35 years of age (a total of 36 cases were <35 years, 52.8% of them were male). The higher mean age of stroke in male cases is likely related to atherosclerotic disease being a more common etiology in men, whereas non-atherosclerotic stroke etiologies are more frequent in female patients.

The three most common risk factors in our cases were similar to the risk factors most frequently reported in young stroke patients in literature (smoking, physical inactivity, HTN, HLD) (8–9). However, when risk factors were analyzed by sex, significant differences were observed in female patients. Anemia, defined as the "fifth cardiovascular risk factor", which has a direct relationship with cerebrovascular events and increases mortality in stroke patients, was as frequent as HTN and much more frequent than smoking in women. The rate of anemia observed in our female patients was considerably higher than the 15–29% reported in the literature for patients with acute stroke (10). It is crucial that physicians across all specialties recognize anemia as a treatable and significant risk factor for ischemic stroke.

Diabetes mellitus was more frequent in both sexes than the rates reported in stroke patients aged 18–55 (9). According to Turkish Statistical Institute (TURKSTAT) 2022 data, 23.6% of women and 16.8% of men in Türkiye are reported to be obese (11). In our patients, obesity was an important risk factor above the population average in both sexes. The obesity rate in female patients was higher than that reported in previous studies on young stroke patients (28.9% vs 22%), while the rate was lower in male patients (19.65% vs 23%) (9).

A study published in 2015 reported that one-third of young stroke patients had a family history of stroke, although this history was not linked to a specific stroke subtype (12). This can be explained by the association of stroke-promoting factors such as HTN with genetic factors, as well as the inheritance of genetic diseases such as sickle cell anemia. Additionally, it is evident that family members sharing similar living conditions are exposed to common environmental risks. In our study, this rate was lower than that reported in the literature.

The rate of alcohol use over the age of 15 reported to be 18.4% for men and 5.9% for women in Türkiye (11). However, national statistics considered alcohol use within the last 12 months as the criterion which does not comply with the criteria for our patients to be considered as alcohol users. Based on these findings, we can conclude that the frequency of alcohol use in our patients was probably higher in men than the population average, but cannot be interpreted in women.

Substance use has been reported as a risk factor in up to 41% of young stroke patients (13). None of our patients reported substance use. This may be due to cultural differences, but this finding is not consistent with national data. According to the data of the Turkish Monitoring and Prevention Center for Drugs and Drug Addiction (TUBIM), the rate of those who tried any illicit drug at least once was reported to be 2.9% in the 15–24 age range, 2.8% in the 24–44 age range and 2.3% in the 44–65 age range (14). Urine toxicology testing is not routinely performed for stroke patients in Türkiye, and socio-cultural factors may prevent patients from disclosing their substance use. It is possible that the substance use data in our patients may not reflect the truth. We believe that routine toxicology testing on arrival would be beneficial in young stroke patients.

Coronary artery disease emerged as a significant risk factor in male patients compared to female patients, likely because atherosclerosis is less common in premenopausal women because of hormonal differences and because smoking and alcohol use, known contributors to atherosclerosis, are more frequent in men (15).

Migraine-induced vasospasm, platelet activation and aggregation, and medications used for migraine treatment are thought to increase stroke risk. Migraine is also associated with rare specific conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), which are causes of ischemic stroke in young patients (9). None of our patients had migraine-induced stroke; however, migraine was an important risk factor, particularly in women, occurring as frequently as DM. Also in three cases, stroke was associated with CADASIL.

The use of OCP in women increases the risk of all types of strokes by changing clotting and inflammation factors, in direct proportion to the amount of estrogen in its content, especially in the presence of smoking, migraine and HTN. However, those containing pure progesterone were not found to be associated with ischemic stroke (16). We can state that OCP use in our female patients was above the population average (8.4% vs 4.8%); however, the specific type of OCP used by our patients was not documented (17). This was one of the limitations of our study as it is unclear how many of our patients were using progesterone-only pills.

Detailed tests related to stroke, such as genetic tests and homocysteine levels, were performed only in patients whose etiology was difficult to determine, so the true prevalence of these risk factors might be higher. In addition, the absence of polysomnography test results in our patients, which were not included in the study, was one of the limiting factors in determining the prevalence of OSA which is a less well-documented risk factor in young stroke patients (9).

Although differences in patient selection criteria, diagnostic protocols, and the epidemiology of the patient population where the study was conducted do not allow for direct comparisons, we can state that the proportions of etiological subgroups in our cases were consistent with the rates reported in the literature to date. Even though we considered the upper age limit higher than many previous studies, the proportion of the LAA group (15.5%) did not differ significantly from the rates reported in the literature (6–21%) (18,19). This was similarly reflected in the proportion of SVO, in which cardiovascular risk factors played a role in many cases (14.5% in our study, 2.5–32.6% in the literature) (20,21). Although these results suggest that 55 years may be an appropriate upper age limit for young stroke, the differences we obtained between female and male patients were noteworthy. In male patients, the proportion of LAA was higher than in female patients, although not reaching statistical significance, and this difference was particularly evident in the SVO group, where it reached statistical significance. While there was no significant difference between the mean age of the etiological groups in female patients, the mean age of the LAA group in male patients was higher than that of the other groups. This pattern was also notable in the etiology of CE cases. Consistent with the literature, septal anomalies were the most frequently detected potential cardioembolic source in our study; however, the results differed when analyzed by sex (5). In male patients, the most frequent cardioembolic source was the hypokinetic and akinetic left ventricle, mostly with CAD etiology, which was significantly more frequent than in female patients (46.2% of CE cases in men, n=12; 6.3% of CE cases in women, n=1).

How should all these findings regarding stroke etiology be interpreted? The practical significance of the young stroke definition is to indicate the

age range at which stroke occurrence is unusual. This allows the physician to prioritize which etiologies to consider and to tailor the history, examination, and diagnostic strategies accordingly. This approach enables a faster, more economical, and less invasive determination of etiology. In this context, the question of at what age a patient is considered young for stroke is important. According to the results of our study, the upper age limit for young stroke is slightly younger in men than in women, probably because of cardiovascular events being less common in premenopausal women and because two well-established risk factors promoting atherosclerosis, alcohol and smoking, are more frequent in male patients. A 2023 study conducted in rural Pennsylvania supports our findings (3). This study, investigating rare and conventional stroke risk factors in large young ischemic stroke cohorts, found the upper age limit for young stroke to be 52 in men and 54 in women. Conducting similar studies with larger patient populations across different geographical regions will help establish a consensus definition for young stroke.

In patients with SODE, the most frequent etiology was cervicocephalic dissections, consistent with previous case series (5,22). Although the literature mostly reports ICA dissections as more frequent than VA dissections, in our study, ICA and VA dissections were observed at similar rates, similar to the study published by Kristensen et al. in 1997 (23). This difference may be related to VA dissections being less frequently detected because of limitations in imaging methods.

In young stroke studies, the proportion of SUE has been reported as 13.3–62.4%, forming the most frequent etiological group (24). In our study, this proportion was close to the lowest rate reported in the literature (13.5%). However, despite being a tertiary center, in the group of SUE, the most frequent reason for undetermined stroke etiology was insufficient investigation because of patients not continuing follow-up. The wide range of etiological factors requires many tests to be performed in a short time. Causes such as infections, vasospasm, AF attacks leading to CE, and dissections may be transient or rapidly recoverable, and if not investigated early, they may not be detected. Some biological tests (e.g., antiphospholipid antibodies for antiphospholipid syndrome) may fluctuate and therefore need to be repeated. It is evident that patients face difficulties in attending regular follow-ups and undergoing numerous laboratory and imaging tests while coping with the disability caused by stroke. We need to develop strategies for how to perform etiological investigations more quickly and effectively. Another possibility is that patients may not fully understand the significance of stroke. Functional recovery results are better in young patients. Some series have reported that up to 90% of patients are independent in all activities of daily living (modified Rankin scale score ≤2) (25). In our patients, the rate of previous stroke was 14%, highlighting the importance of determining etiology and protecting patients with appropriate secondary prevention strategies. Patients should be informed about the importance of clarifying stroke etiology to assess the risk of recurrent stroke and determine secondary prevention strategies.

In conclusion, according to our study findings, stroke risk factors and etiology differed significantly between young female and male stroke patients. Traditional vascular risk factors and etiologies were more frequent in male patients, and the age at stroke onset was likely higher because of this. These findings suggest that the upper age cutoff used in the definition of young stroke should differ between women and men, and that developing sex-specific strategies in screening and controlling risk factors, as well as selecting etiological investigations, would be beneficial.

The main limitations of this study are its single-center design, the lack of a broad patient population, and the fact that the prevalence of risk factors was not compared with healthy adults of the same age range and similar sex distribution. The absence of routine toxicology testing in patients, the inability to determine the type of OCP used by female patients, the exclusion of formal sleep study results for suspected SRBDs in a significant portion of patients, and the lack of review of vascular imaging for carotid webs, which were recently reported to potentially cause ischemic strokes, represent other limitations of the study (9).

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