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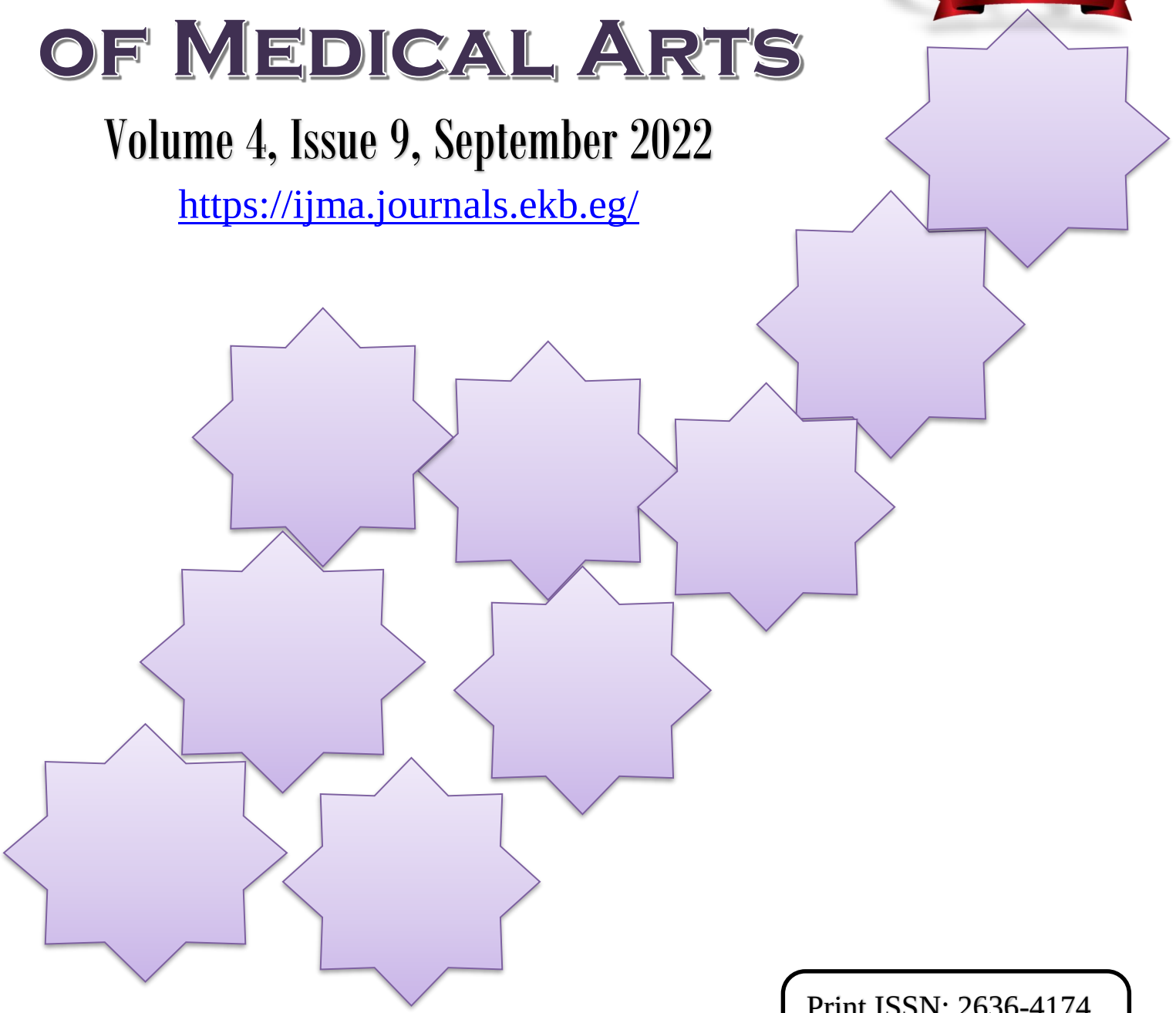

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Original Article

Neurovascular Findings and Associated Risk Factors in Stroke in Young and Middle-Aged Patients: A Single Center Experience

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ABSTRACT

Background: The increasing incidence of stroke in younger people underscores the urgent need for research to elucidate the underlying risk factors and causes. To date, the vast majority of studies of stroke in young people have been conducted in European and North American regions.

Aim of the work: To characterize the neurovascular findings and associated risk factors for stroke in young and middle-aged patients at Almoosa Hospital in Saudi Arabia.

Methods: We retrospectively analyzed data from consecutive patients with ischemic stroke and transient ischemic attack aged 25 to 60 years who underwent detailed cardiocerebrovascular examination.

Results: The study included 182 patients, most of whom [89%] presented with stroke and 11% with transient ischemic attack. The mean age was 51.2±8.4 years [25-60 years], 62.6% were men, mean BMI was 30.7±5.4, 41.2% were smokers, 52.7% were diabetic, 60.4% had hypertension, and 38.5% had dyslipidemia. Cardiac risk factors were valvular heart disease [34.1%], ischemic heart disease [16.5%], cardiac thrombi [8.8%], and septal defects [4.4%]. Magnetic resonance imaging revealed anterior circulation infarction in 47.3% and posterior circulation infarction in 14.3%, whereas both anterior and posterior circulation infarction were found in 27.5%. Neurovascular imaging of the neck was performed in 102 patients, with 16.5% having mild stenosis, 7.7% moderate stenosis, 9.9% severe stenosis 8.8%, and 5.5% complete stenosis. Carotid arteries duplex examination revealed insignificant stenosis in 15.4% and significant stenosis in 6.6%. Type 2 diabetes, hypertension, and dyslipidemia had a major impact on the extent of stenosis, whereas DM 2 and dyslipidemia were significantly more common in patients with increasing degrees of stenosis.

Conclusion: In this study young patients with ischemic stroke had different cerebrovascular risk factors and etiologies compared with previous cohorts, indicating the need for tailored prevention interventions that take into account regional epidemiological data on cerebrovascular health.

Keywords: Stroke; Cerebrovascular accident; Ischemic stroke; Extracranial artery stenosis; Intracranial artery stenosis.

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INTRODUCTION

Ischemic stroke is a major cause of long-term disability and has a profound impact on the quality of life of patients and caregivers. In both developing and developed countries, the incidence of stroke at a young age is increasing; an estimated 10% to 20% of these events occur in young people and are associated with high morbidity and mortality and long-term psychological, physical, and social consequences [1].

In Saudi Arabia, acute stroke is a common condition with an incidence of 30-40/1,00,000 per year and a prevalence of 186/1,00,000 [2-4]. The main risk factor for stroke is hypertension [5], and other risk factors include high cholesterol, tobacco smoking, obesity, diabetes mellitus, previous TIAs, end-stage renal disease, alcohol abuse, and atrial fibrillation [6]. The World Health Organization defines young age as 25 to 44 years and middle age as 44 to 60 years [7]. Young adults experience more ischemic infarcts from known causes [up to 34%], and cardioembolism [up to 46%], dissection, vasculitis, or vasospasm are more common at this age than in the elderly. These infarcts are less likely to be caused by large or small vessel disease [8, 9]. In Saudi Arabia, hypertension, hyperlipidemia, obesity, type 2 diabetes, ischemic heart disease, atrial fibrillation, smoking, and physical inactivity increase the risk of stroke [2]. In other studies, smoking [56%], physical inactivity [48%], hypertension [47%], and dyslipidemia [35%] are the most common risk factors for ischemic stroke in young patients [10, 11].

Cardiac emboli account for nearly 30% of ischemic strokes in young adults, mostly due to congenital cardiac anomalies [patent foramen ovale, atrial septal aneurysms], nonrheumatic valvular heart disease, and cardiomyopathies [12]. Predisposing factors for cervicocephalic arterial dissection are common: hypertension, recent infections, and migraine. They are the cause of 20% of ischemic strokes in young patients and occur more frequently in men [52-69%] [13]. Numerous hematologic disorders predispose to stroke: leukemia, intravascular lymphoma, sickle cell disease, erythrocytosis, and polycythemia vera. Coagulopathies such as protein C, protein S, antithrombin deficiency, and factor V Leiden mutation are most commonly associated with venous thrombosis, but the risk of arterial thrombosis is also increased [14].

Atherosclerosis is the leading cause of internal carotid artery stenosis, which is responsible for 8-15% of ischemic strokes [symptomatic carotid artery stenosis] [15]. Extracranial artery stenosis [ECAS] is a common condition worldwide and one of the most important risk factors for ischemic stroke [15]. Intracranial stenosis is a very common cause of stroke worldwide with significant ethnic differences. Intracranial stenoses are common in older age and are frequently detected with the increasing use of noninvasive angiography, but have been neglected as a cause of stroke in Caucasians [16].

AIM OF THE WORK

The aim of this study is to highlight new findings and advances in the prevalence of neurovascular findings and their correlation with other traditional risk factors in young and middle-aged patients with ischemic stroke/TIA.

PATIENTS AND METHODS

This was a cross-sectional observational study conducted at Almoosa Specialist Hospital from August 2017 to August 2019. It was established in 1996 as the first private hospital in Al Ahsa in Eastern Province. Almoosa Specialist Hospital is an academic teaching hospital accredited by the Saudi Health Specialties Commission and has a capacity of over 400 beds. Ethical approval was obtained from the Institutional Review Board of our hospital [IRB log number: ARC -22.03.3]. Patients had hyperacute or acute focal neurologic deficits observed in the inpatient and outpatient areas of the hospital. Patient consent and ethical approval were obtained from the Institutional Review Board of our hospital.

Study Population: All patients who visited our hospital during the study period with the chief complaint of transient or established hyperacute or acute neurologic deficit of less than one week were included in the study. The exclusion criteria: 1. age less than 25 and more than 60 years, 2. diagnosis of intracerebral hemorrhage or neoplasm, 3. mimic stroke, 4. subacute or chronic ischemic stroke.

All cases with severe ischemic stroke were admitted to the intensive care unit for observation and treatment and transferred to the medical ward after stabilization. Demographic data collected were: Age, sex, height, weight,

BMI, ethanol abuse, concomitant diseases [such as type 2 diabetes, hypertension, ischemic heart disease, lung disease, migraine, kidney disease], thyroid disease, sickle cell disease and connective tissue disease, and epilepsy].

The following laboratory tests were performed in all patients: Blood glucose and coagulation profile, complete blood count [CBC], renal and liver function tests, fasting lipid profile, electroencephalography [ECG]. Pregnancy testing for female patients [of childbearing age]. In some cases: cardiac biomarkers, erythrocyte sedimentation rate, antinuclear antibodies [ANA], rheumatoid factor, homocysteine levels, thrombophilia [to exclude factor V Leiden mutation, prothrombin gene mutation, protein C and S deficiency and ATIII deficiency, and antiphospholipid antibody syndrome], and sickle cell test.

Computed tomography of the brain [CT] offers several logistical advantages for patients with acute stroke, is essential for exclusion of mimics and chameleons [intracranial masses, hemorrhage], and possible confirmation of the diagnosis of ischemic stroke. Image acquisition is faster, easily accessible, and usually occurs in the emergency department, allowing testing with non-contrast scanning CT, CT angiography [CTA], and CT perfusion scanning in a short time [14]. Magnetic resonance angiography [MRA] is an important advance in neuro-imaging for stroke that provides great structural detail, can detect early cerebral edema, and is sensitive for detecting acute intracranial hemorrhage. However, MRI is not available in emergencies to the same extent as CT, many patients have contraindications to MRI imaging [e.g., pacemakers, implants], and interpretation of MRI scans can be more difficult [14].

Duplex examination of the carotid artery is one of the most useful investigations in the evaluation of patients with stroke because it is accessible, noninvasive, and inexpensive to detect carotid stenosis. It is increasingly made earlier in the evaluation, not only to determine the cause of the stroke but also to stratify patients for either drug treatment or carotid intervention if they have carotid stenosis [14].

Transthoracic echocardiography was performed in some patients to obtain comprehensive information on the risk of thromboembolism in stroke, and trans-esophageal echocardiography was performed in selected cases [high proportion of emboli, patients with metal valve prostheses, suspected intracardiac shunt, and poor echo window] [14].

Statistical Analysis: The study was performed with the SPSS computer package version 25.0 [IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp., USA]. For descriptive statistics, mean ± SD was used for quantitative variables, and frequency and percentage were used for qualitative variables. The chi-square test was used to evaluate the differences in the frequency of the qualitative variables, whereas the Kruskal-Walli's test was used to evaluate the differences in the means of the quantitative nonparametric variables. The statistical methods were tested assuming a significance level of $p < 0.05$..

RESULTS

The study included 182 patients who met the inclusion criteria, with a mean age of 51.2 ± 8.4 years between 25 and 60 years, 61 [33.5%] aged 25 to 45 years, and 121 [66.5%] aged 45 to 60 years. Ninety-nine [59.9%] were men and 73 [40.1%] were women, and the mean BMI was 30.9 ± 5.6 and ranged from 16.2to 49.8 kg/m^2. The majority of patients [162; 89%] presented with stroke and 20 [11%] with TIAs. Seventy-five patients [41.2%] were smokers, 96 [52.7%] were diabetic, 110 [60.4%] were hypertensive, and 70 [38.5%] had dyslipidemia [Table 1].

MRI findings showed anterior circulation infarction in 86 patients [47.3%], posterior circulation infarction in 26 patients [14.3%], whereas both anterior and posterior circulation infarction were detected in 50 patients [27.5%]. These infarcts were higher on MRI than on CT. Neurovascular imaging of the neck revealed mild stenosis in 56 patients [30.8%], moderate stenosis in 30 [16.5%], severe stenosis in 23 [12.6%], complete stenosis in 8 [4.4%], aortic arteritis in 4 [2.2%], and dissection in 2 [1.1%]. Neurovascular imaging of the head revealed mild stenosis in 54 [29.7%] patients, moderate stenosis in 50 [27.5%], severe stenosis in 20 [11.0%], and complete stenosis in 16 [8.8%], while 2 patients [1.1%] had myomyoma disease and 2 others [1.1%] had arteritis of the great vessels. Neck duplex examination revealed insignificant stenosis in 28 [15.4%] and significant stenosis in 12 [6.6%] [Table 2].

Cardiac risk factors for cerebrovascular accidents were valvular heart disease in 62

patients [34.1%], ischemic heart disease in 30 [16.5%], cardiac thrombi in 16 [8.8%], and septal defects in 8 [4.4%]. Other risk factors included migraine, sickle disease in 8 patients each [4.4%] and bronchial asthma, post-meningitis, pulmonary TB, hypothyroidism and homocysteineemia in 2 patients each [1.1%] [Table 3 & Figure 1]

On imaging of the neck, age, sex, and smoking didn't affect the degree of stenosis. However, BMI, DM2, HTN, and dyslipidemia had a significant effect on the degree of stenosis, with a higher risk in those with a higher degree of stenosis [Table 4].

Imaging of the head did not reveal significant differences between the different degrees of stenosis in terms of age, sex, and BMI. On the other hand, smoking, DM, HTN, and dyslipidemia were significantly more common in patients with increasing degrees of stenosis. Dyslipidemia was a significantly higher risk factor [table 5].

Table [1]: Demographics and comorbidities of the studied sample

Variable		Total [n=182]
Age [years]	Mean ± SD	51.2 ± 8.4
	Min – Max	25 – 60
	25 – 45 years	61 [33.5]
	45 – 60 years	121 [66.5]
Gender, n [%]	Male	109 [59.9]
	Female	73 [40.1]
BMI [kg/m^2]	Mean ± SD	30.9 ± 5.6
	Min – Max	16.2 – 49.8
Clinical findings, n [%]	Stroke	162 [89.0]
	TIAs	20 [11.0]
Smoking, n [%]		75 [41.2]
Diabetes mellitus, n [%]		96 [52.7]
Hypertension, n [%]		110 [60.4]
Dyslipidemia, n [%]		70 [38.5]

Table [2]: Neurovascular imaging findings of the studied sample

	Variable	Total [n=182], No. [%]
CT Findings	Normal	80 [44.0]
	Anterior circulation infarction	58 [31.9]
	Posterior circulation infarction	20 [11.0]
	Anterior and posterior circulation infarctions	24 [13.2]
MRI Findings	Normal	20 [11.0]
	Anterior circulation infarction	86 [47.3]
	Posterior circulation infarction	26 [14.3]
	Anterior and posterior circulation infarctions	50 [27.5]
Neck imaging	Normal	59 [32.4]
	Mild stenosis [< 50%]	56 [30.8]
	Moderate stenosis [50 – 69%]	30 [16.5]
	Severe stenosis [70 – 99%]	23 [12.6]
	Total stenosis [100%]	8 [4.4]
	Aortic arteritis	4 [2.2]
	Dissection	2 [1.1]
Head imaging	Normal	38 [20.9]
	Mild stenosis [< 50%]	54 [29.7]
	Moderate stenosis [50 – 69%]	50 [27.5]
	Severe stenosis [70 – 99%]	20 [11.0]
	Total stenosis [100%]	16 [8.8]
	Myomyoma disease	2 [1.1]
	Large vessel arteritis	2 [1.1]
Neck duplex	Normal	74 [40.7]
	Insignificant stenosis [<50%]	28 [15.4]
	Significant stenosis [> 50%]	12 [6.6]
	Not done	68 [37.4]

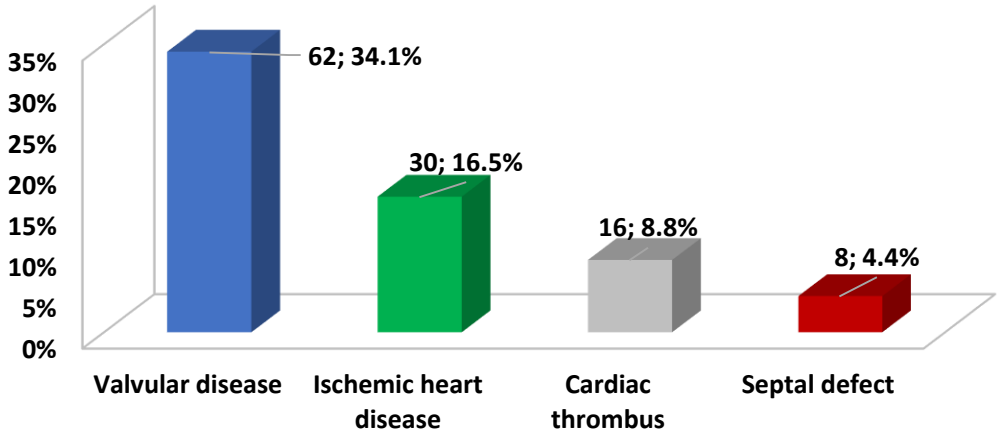

Figure [1]: Cardiac causes as risk factors for cerebrovascular accidents among the studied sample

Table [3]: Other risk factors for cerebrovascular accidents among the studied sample

Other risk factors	Total [n=182], No. [%]
Migraine [± aura]	8 [4.4]
Bronchial asthma	2 [1.1]
Post-meningitis	2 [1.1]
Pulmonary TB	2 [1.1]
Dyspepsia related GIT disease	2 [1.1]
Sickle disease	8 [4.4]
Hypothyroidism	2 [1.1]
Homocysteinemia	2 [1.1]

Table [4]: Relation between stenosis by neck imaging and different study variables

Variables	Normal n=59	Mild n=56	Moderate n=30	Severe n=23	Total n=8	P-value
Age [years]						
25 – 45 yrs	22 [37.3]	21 [37.5]	7 [23.3]	7 [30.4]	3 [37.5]	0.684
45 – 60 yrs	35 [59.3]	35 [62.5]	25 [83.3]	16 [69.6]	5 [62.5]	
Gender						
Male	30 [50.8]	35 [62.5]	16 [53.3]	19 [82.6]	6 [75.0]	0.077
Female	29 [49.2]	21 [37.5]	14 [46.7]	4 [17.4]	2 [25.0]	
BMI [kg/m^2]	28.3 ± 4.6	30.6 ± 6.4	30.8 ± 4.4	31. °± 5.9	33.3 ± 4.7	**0.22***
Smoking	18 [30.5]	29 [51.8]	13 [43.3]	10 [43.5]	5 [62.5]	0.149
Diabetes mellitus	19 [32.2]	35 [62.5]	20 [66.7]	16 [69.6]	6 [75.0]	**0.001***
Hypertension	28 [47.5]	35 [62.5]	22 [73.3]	18 [78.3]	7 [87.5]	**0.019***
Dyslipidemia	15 [25.4]	23 [41.1]	14 [46.7]	13 [56.5]	5 [62.5]	**0.038***

Table [5]: Relation between stenosis by head imaging and different study variables

Variables	Normal n=38	Mild n=54	Moderate n=50	Severe n=20	Total n=16	P-value
Age [years]						**0.990**
25 – 45 yrs	14 [36.8]	18 [33.3]	16 [32.0]	7 [35.0]	5 [31.3]	
45 – 60 yrs	24 [63.2]	36 [66.7]	34 [68.0]	13 [65.0]	11 [68.8]	
Gender						**0.793**
Male	21 [55.3]	32 [59.3]	30 [60.0]	14 [70.0]	11 [68.8]	
Female	17 [44.7]	22 [40.7]	20 [40.0]	6 [30.0]	5 [31.3]	
BMI [kg/m^2]	29.9 ± 4.5	30.9 ± 5.1	29.5 ± 5.6	30.9 ± 6.3	33.0 ± 5.6	**0.189**
Smoking	11 [28.9]	20 [37.0]	20 [40.0]	13 [65.0]	11 [68.8]	**0.015***
Diabetes mellitus	10 [26.3]	28 [51.9]	31 [62.0]	14 [70.0]	13 [81.3]	**0.001***
Hypertension	13 [34.2]	35 [64.8]	36 [72.0]	14 [70.0]	12 [75.0]	**0.٠٠٣***
Dyslipidemia	4 [10.5]	13 [24.1]	29 [58.6]	13 [65.0]	11 [68.8]	**<0.001***

DISCUSSION

Because ischemic strokes occur less frequently in younger adults [10% to 14%], the pathogenesis of strokes in younger adults must take into account several less common risk factors to identify or narrow down a list of possible pathogeneses, which is critical for preventing recurrent strokes in younger adults requiring evaluation for hypercoagulable causes, vascular imaging, and echocardiography. Young stroke survivors have high rates of traditional risk factors. These risk factors should be treated aggressively to reduce long-term risk [9, 17].

In this study, the mean age was 51.2±8.4 years, 62.6% of patients were male, and the mean BMI was 30.7±5.4. The majority of patients [89%] had stroke and [11%] TIAs. The main concomitant diseases were: smokers [41.2%], diabetics [52.7%], hypertensive [60.4%], and 70 [38.5%] had dyslipidemia. Ischemic stroke is more common in younger adults, and the traditional stroke risk factors typically found in older adults [hypertension, hyperlipidemia, diabetes mellitus, tobacco use, and obesity] also occur in younger patients with acute stroke [18-20]. Smoking is even more prevalent in younger stroke patients than in older adults [20]. One study reported the prevalence of dyslipidemia [38%], smoking [34%], hypertension [20%], and diabetes mellitus [11%] [21]. The modifiable risk factors associated with stroke in Saudi Arabia are usually divided into modifiable factors such as hypertension, diabetes mellitus types 1 and 2, cardiovascular disease, hyperlipidemia, atrial fibrillation, physical inactivity, obesity, smoking, and alcohol consumption [22].

In one study, about forty percent of stroke patients had hypertension with diabetes, 24.9 percent had hypertension and 11.6 percent had diabetes mellitus [23]. In another study, hypertension [45.6%], diabetes mellitus [22.8%], and heart disease with or without atrial fibrillation [1.1%] were among the most important risk factors [24].

In another study, essential hypertension, type 2 diabetes mellitus, hyperlipidemia, and obesity were identified as major risk factors [25]. Similarly, a close association between stroke and essential hypertension has been reported in several studies worldwide. The apparent interaction between hypertension and other risk factors [dyslipidemia, type 2 diabetes, obesity, and smoking] substantially increases the cumulative risk of stroke in patients with hypertension [26].

Wu *et al.* [27] reported that hypertension accounted for 52.4%, type 2 diabetes 48.4%, hyperlipidemia 58.1%, and a history of coronary heart disease or stroke 54.3%. Obesity is considered one of the most important modifiable risk factors for ischemic stroke, and its prevalence is 34% in the United States and 20% in several European countries [28, 29]. A systematic review study reported that obesity is a common risk factor [5.3% - 66.0%] for stroke in Middle Eastern countries [30]. The age and sex distribution in this study is similar to other studies with a similar age range [1, 31]. However, a higher proportion of men was observed in studies with a higher age cutoff [32]. Considering sex differences, the incidence appears to be higher in men than in women, although some studies have shown that the incidence of "young stroke" is higher in women before 30 years of age. Men have been found to have a higher mortality rate and a higher risk of recurrent vascular events [33, 34]. Conflicting results have been reported on the incidence in men and women. Several studies from Europe and the United States showed a higher incidence in women younger than 30 and 44 years, respectively **[35-38]**. In contrast, incidence rates in France were similar in both sexes [18 to 55 years], and in Spain, incidence was higher in men [18 to 54 years] [39]. In Chinese adults [aged 20 to 49 years], there were no statistical differences in the age-standardized prevalence of ischemic stroke between men and women [40].

In this study, the cardiac risk factors for cerebrovascular accidents were valvular heart disease [34.1%], ischemic heart disease [16.5%], cardiac thrombi [8.8%], and septal defects [4.4%]. Other risk factors were migraine in 8 patients [4.4%], sickle cell disease, and homocysteinemia in 1.1% each. In the cohort study, hyperlipidemia [71.4%] and small vessel occlusion [31.7%] had the highest prevalence, followed by type 2 diabetes [52.4%] and cardioembolism [19%]. In very young patients, the most common cause was cardioembolism [27.3%] [40]. Analysis of risk factors by sex showed that cardiovascular disease was more common in men than in women, an observation also consistent with previous studies [41, 42]. Studies of stroke subtypes reported a wide range and slightly higher prevalence [20-47%] of cardio-embolism in younger stroke patients

compared with all ischemic stroke patients [20-25%] [43, 44]. Cardio-embolic stroke is the most common subtype in young adults, accounting for up to 46% of ischemic infarcts in this age group [45]. Cardio-embolic stroke occurred in 47% [including 17% with isolated foramen ovale], and the cause of stroke was unclear in 11%. Relevant abnormalities were detected in 100 of 195 patients by cardiac ultrasound and in 30 of 189 patients by hypercoagulability panel [9].

In a study of 2,634 patients with ischemic stroke, it was reported that the most common causes of cardioembolic stroke were valvular heart disease associated with rheumatic heart disease [44 patients, 70.1%], cardiomyopathy in 4 [6%] patients, atrial fibrillation in 4 [6%], and other causes in 16.1% [infective endocarditis in 4 and myocardial infarction in 6] [46]. **Wu *et al.*** [27] found that 4% of strokes in adolescents were due to cardiogenic cerebral embolism [because of the absence of transesophageal sonography and TCD foam testing]. It is suggested that screening for cardiogenic stroke should be routinely performed in the future to allow individualized treatment.

In this study, neurovascular imaging of the head was performed in 110 patients, and 45.6% were found to have stenosis, [18.7%] mild, [13.2%] moderate, [8.8%] severe, and [5.5%] complete. Inflammation of the aortic artery was found in [2.2%] and dissection in [1.1%]. Duplex examination of the carotid arteries revealed insignificant stenosis in 28 [15.4%] and significant stenosis in 12 [6.6%]. **Hurford *et al.*** [47] performed a systematic review and identified 28 studies on the prevalence of ICS in Caucasian stroke and TIA patients. These studies found that [12.1%] had ICS, [6.4%] had symptomatic ICS, and [11.1%] had asymptomatic ICS [15]. In a population-based Oxford study of 1368 Caucasian patients with minor ischemic stroke and TIA, 6.9% had symptomatic 50-99% ICS, and this was highly age-dependent [4.7% at < 50 years].

in this study, an ICA stenosis of > 50% is considered a discriminator between significant and non-significant stenosis and may require annual follow-up by carotid ultrasound. This is in line with **Ong *et al.*** [38]. ICAS is one of the most common causes of ischemic stroke and accounts for 30% to 50% of ischemic strokes in Asia [16]. International guidelines recommend screening for extracranial stenosis of the internal carotid artery for secondary prevention of stroke [10, 30], but the benefit of routine screening for intracranial stenosis has not been established [48, 49].

Chronic systemic disease [19.2%], chronic head and neck disease [14.6%], heart disease [13.9%], and arteriopathy [12.2%] were the most frequently cited risk factors in patients with young stroke [50].

Study limitations: The study design was limiting because it was a retrospective study at a single center, the sample size was not large enough, and scores for disease severity using validated scales were not available. The anamnesis of the alcohol abuse was not taken for legal-medical and insurance-legal reasons.

Conclusions: Our group of young stroke patients had different cerebrovascular risk profiles and stroke etiologies compared with previous cohorts, indicating the need for tailored prevention interventions that also take into account regional epidemiological data on cerebrovascular health.

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Conflicts of interest: No conflicts of interest exist.

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