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RISK FACTORS OF ISCHEMIC STROKE IN YOUNG ADULTS OF PAKISTAN

Yasir Akbar Jamali[1]*, Jamshed Warsi[1], Zulfiqar Ali Laghari[1]

[1]Department of Physiology, University of Sindh, Jamshoro – Pakistan

***Correspondence Author:** - Yasir Akbar Jamali
*Department of Physiology, University of Sindh, Jamshoro, Email: - Yasirakbar021@gmail.com

Abstract
Background: Although most stroke patients are above the age of 65, 10% of stroke victims are estimated to be under the age of 45. There is evidence that young individuals are experiencing an increasing rate of ischemic stroke, while the reasons for this rise are unclear. Stroke in younger people calls for different research and treatment than in older people. Neurosonology aids in the diagnosis and post-interventional assessment of carotid artery disease in patients having carotid revascularization procedures.
Objective: This study aimed to study the incidence and risk factors of ischemic stroke in young adults**.**
Patients and Methods: We recruited patients with ischemic stroke older than 18 years and younger than 45 years admitted to medical wards I, II, and III, PUMHS Hospital, within the first week of the acute event.
Results: Analysis was done for 151 (72.2%) ischemic strokes out of 209 young stroke patients. The most common risk factors for ischemic stroke included hypertension in 75 (49.7%), followed by diabetes mellitus in 32 (21.2%). Cardiac disease, smoking, and previous stroke were found in 18 (11.9%), 14 (9.3%), and 21 (13.9%) patients, respectively. The mean GCS score of ischemic stroke patients was 10.6 ± 3.7. The mean GCS score indicated mild ischemic stroke.
Conclusion: The findings of this study showed that predominant risk factors for ischemic stroke among young people in the local area include hypertension, diabetes mellitus, cardiac disease, and smoking.

Keywords: Ischemic Stroke, Cerebral infarction, Young adults, risk factors, Pakistan

Introduction

Hospitalization rates and the overall incidence of acute ischemic stroke among young individuals are on the rise, in contrast to the declining rates seen in the elderly [1]. High hospitalization expenses and lost productivity due to strokes in young adults have been reported to have grown by as much as 40% worldwide over the previous few decades [1].
About 85% of all deaths occur in underdeveloped nations due to this [2]. It was revealed that most research on ischemic stroke in young people was done in industrialized nationsThe occurrence of ischemic stroke in young individuals in South Asia is relatively infrequent. However, few research has been recorded, and stroke is seen as an unrecognized burden in this region [3]. Pakistan, Nepal, Afghanistan, Bhutan, Bangladesh, Iran, Srilanka, India, and Iran are all considered part of South Asia by the United Nations' statistical office [4]. The region of South Asia encompasses a significant portion,

over one-fifth, of the global population, with its inhabitants dispersed across many locations across the globe [3]. As a result of high population density and their location inside economically disadvantaged areas, a significant portion of the population in these nations continues to lack access to adequate educational institutions. As a result, individuals lack awareness of modifiable risk factors such as hypertension, smoking, diabetes, alcohol usage, and the limited availability of healthcare facilities and personnel. Research has shown a greater prevalence of young individuals experiencing strokes in these specific places when compared to Western nations [5], [6]. The study revealed that stroke patients from South Asia had a much younger age profile compared to stroke patients residing in Western nations [7], [8].

Moreover, some investigations have shown an increased susceptibility to ischemic stroke among individuals aged 30 to 45 [9], [10]. Despite the limited availability of epidemiological data pertaining to the Pakistani population, a small number of hospital-based studies have shown an elevated incidence of stroke among young individuals within this demographic. According to a clinical research conducted by Khan JA et al., it was observed that the occurrence of stroke was more prevalent among those aged between 15 and 45 years, with a reported incidence rate of 26% [11]. Additionally, Vohra et al. conducted a case series investigation which revealed that 34% of the stroke patients included in their analysis were younger than 50 years of age [12]. Stroke is a global health issue, yet it seems that more than two-thirds of the burden falls on underdeveloped nations [13]. While just 3-8% of strokes occur in the West's young adults, 10%-30% of strokes occur in India's youth [14]–[16]. Likewise, there is a notable prevalence of stroke among the younger population in Pakistan, which has the potential to result in a significant economic burden. Furthermore, available research indicates that hypertension has been identified as the most often observed risk factor among young patients [17], [18]. Therefore, it is essential to assess the risk factors and etiology of stroke in young individuals in order to mitigate disability and recurrent strokes within this demographic [18], [19].

In the context of developing countries, there exists a dearth of data pertaining to stroke occurrences among young individuals, despite the escalating prevalence of this issue. Nevertheless, conducting research in these regions is important in order to effectively strategize for the implementation of suitable screening, diagnostic, and therapeutic measures. Determining an age threshold may be challenging and susceptible to interpretation. However, existing research and registries often classify young adults as those below the age of 55 [20].

Therefore, the goal of our study was to investigate the incidence and risk factors of ischemic stroke in young adults in Pakistan.

Methodology

The present investigation was carried out in the Medical Units I, II, and III of the Peoples University of Medical and Health Sciences for Women Nawabshah, Sindh, Pakistan, spanning from September 2021 to June 2023. This research excluded individuals under the age of 18 years and those beyond the age of 45 years with brain damage or head trauma. The current study had a cohort of 151 participants, including persons of both genders, ranging in age from 18 to 45 years, who underwent therapy for ischemic stroke. The information needed to gather the data was extracted from a variety of sources, including medical records, patient records, laboratory investigations, diagnostic tests, radiographic pictures, and reports, amongst others. At admission, the patient's level of consciousness was evaluated using the Glasgow Coma Scale (GCS). Following approval from the institutional review board and consent from patients or their legal guardians, a thorough set of demographic data was collected. This was done before any data was ever collected. Individuals' ages, places of residence, socioeconomic status, and sexes were just some of the details that were documented using the authorized proforma. All study subjects initially underwent a battery of diagnostic procedures. The erythrocyte sedimentation rate (ESR), complete blood count (CBC), liver function test (LFT), hemoglobin a1c in the urine, kidney function tests, and lipid profile were among the tests performed. Echocardiography, carotid Doppler, and electrocardiogram (ECG) monitoring were

also performed, along with other medical treatments, over the course of 24 hours. At the time of arrival, each patient underwent a computed tomography (CT) brain scan. When an MRI scan of the patient's brain was deemed required, a stroke procedure was used.

In addition, a glycosylated hemoglobin level of less than 6.5% can be used to distinguish diabetes mellitus from other forms of the disease in those who take insulin or oral hypoglycemic medicines. The statistical data analysis was performed using SPSS V24. When comparing two sets of categorical data, the Chi-square test is used to determine statistical significance. Statistical computations were conducted to ascertain the percentage, mean, and standard deviation of all variables. A p-value less than 0.05 was considered to have statistical significance.

Results

The total number of patients with ischemic stroke was 151 (72.2%) out of 209. Male and female patients were 69 (45.7%) and 82 (54.3%). The mean GCS score of patients with ischemic stroke was 10.6 ± 3.7. The mean age of the patients was 38.7 ± 7.3 years.

The most common risk factor was hypertension 75 (49.7%). Ischemic stroke and hypertension have a significant relationship (p = 0.001). Thirty-two (21.2%) had diabetes mellitus significantly associated with ischemic stroke (p = 0.027). Cardiac diseases were found in 33 (21.9%) patients and were significantly associated with ischemic stroke (p = 0.001). Smoking was also a significant risk factor, with 14 (9.3%) patients (p = 0.029). Twenty-one (13.9%) of the patients had a substantial history of previous stroke (p = 0.045) Table 1.

Table 1. Risk factors for young patients with ischemic stroke

Risk Factors	**Yes**	**No**	**P value**
Hypertension	75 (49.7%)	76 (49.7%)	0.001
Diabetes Mellitus	32 (21.2%)	119 (78.8%)	0.027
Smoker	14 (9.3%)	137 (90.7%)	0.029
Alcohol	3 (2.0%)	148 (98.0%)	0.999
Eclampsia	2 (1.3%)	149 (98.7%)	0.828
Cerebral venous thrombus	2 (1.3%)	149 (98.7%)	0.828
Cortical venous thrombus	4 (2.6%)	147 (97.4%)	0.999
Cerebral venous sinuous thrombus	1 (0.7%)	150 (99.3%)	0.174
Vascular Ehlers-Danlos syndrome	1 (0.7)	150 (99.3%)	1.000
Atherosclerosis	13 (8.6%)	138 (91.4%)	1.000
Past stroke	21 (13.9%)	130 (86.1%)	0.067
Migraine	2 (1.3%)	149 (98.7%)	1.000
Postpartum	3 (2.0%)	148 (98.0%)	0.999
Small vessel disease	21 (13.9%)	130 (86.1%)	0.032
Aneurysm	1 (0.7%)	150 (99.3%)	1.000
Cardiac Diseases[a]	33 (21.9%)	118 (78.1%)	0.001
Aortic stenosis	1 (0.7%)	150 (99.3%)	1.000
Coronary artery disease	1 (0.7%)	150 (99.3%)	1.000
Ischemic heart disease	6 (4.0%)	145 (96.0%)	0.999
Arterial fibrillation	4 (2.6%)	147 (97.4%)	0.999
Myocardial infarction	6 (4.0%)	145 (96.0%)	0.999
Heart failure	8 (6.0%)	142 (94.0%)	0.999
PFO	7 (4.6%)	144 (95.4%)	0.999

PFO, patent foramen ovale

[a] Aortic stenosis, coronary heart disease, ischemic heart disease, heart failure, arterial

fibrillation, myocardial infarction, heart failure and PFO

Alcohol history was found in 3 (2.0%) of patients. Two (1.3%) patients had eclampsia. Arterial fibrillation was reported in 4 (2.6%) of patients. Cerebral and cortical venous thrombus was observed in 2 (1.3%) and 4 (2.6%) patients. Myocardial infarction in 6 (4.0%) of the patients. Migraine in 2 (1.3%) of patients. Atherosclerosis in 13 (8.6%). Aneurysm, cerebral venous sinuous thrombus, vascular Ehlers-Danlos syndrome, aneurysm, and aortic stenosis were observed in one (0.7%) each. Heart failure and PFO were found in 9 (6.0%) and 7 (4.6%) patients, respectively Table 1.
We compared patients aged 18 – 30 28 (18.5%) with those aged 31 – 45 123 (81.5%). Ischemic stroke was particularly more prevalent in patients aged 31 – 45 years than in those aged 18 – 30 years (123 (81.5%) vs 28 (18.5%)).

Discussion

In our study, the incidence of patients with ischemic stroke was 151 (72.2%). Previous studies were in agreement with our research; they found that the majority of incident cases of stroke are ischemic stroke (87%) and (71.9%) [21], (71.97%) were described as an ischemic type [22]
In the present study, most of our sixty-two (41.1%) patients were classified as moderate ischemic stroke as measured by GCS at admission. This is in agreement with Rasha et al. [23], Li et al. [24], and Lutski et al. [25] in Egypt, Israel, and China, respectively, who found that most strokes in young adults were mild.
Our study discovered that women outnumbered men in the present study [(52.9% vs 47.15%)]. The female preponderance was consistent with studies by Barinagarrementeria *et al.* and Yesilot *et al.*, which revealed that women had a greater stroke incidence than males did in the age range of 18 to 34, with the trend reversing in the age range of 35 to 49 [26], [27].El Tellawy *et al.* described female predominance among this age group (20 to <40 years of age) in their study on stroke epidemiology in Upper Egypt [28].
In this study, we found that the most common risk factor was hypertension 75 (49.7%). Ge et al. and Xu et al. observed a higher prevalence of hypertension, 60.0% and 58.6% in ischemic stroke patients, respectively [29], [30]. In comparison, two studies reported lower prevalence of hypertension, 29.8% and 36.7% [31], [32].
In our study, smoking was also a significant risk factor, with 14 (9.3%) patients, which is nearly similar to Sayedahmed et al., who reported (10.7%) of patients found with history of smoking [31]. In contrast, other studies found higher prevalence of smoking (50.0%) [33], (49.6%) [34], (60%) [32] (41%) [30].
In the current study, history of alcohol was only found in 3 (2.0%) of patients, which is lower than previous studies that reported history of alcohol in patients from (7.0%) to (49.0%) [21], [29], [30], [34], [35]
32 (21.2%) of the study patients had diabetes mellitus, which is higher than Sayed et al., Ramirez-Moreno et al., Amaya et al., and Ekker et al., who found that DM was present in (13.1%), (13.3%), (10.5%) and (10.4%), respectively [21], [31], [34], [36].
In our study, cardiac disease was found in 18 (11.9%), which is nearly similar to Tang et al., who reported heart disease in (10.4%) of patients [37]. Namaganda et al. reported a lower prevalence (3.9%) of patients [38]. Although, some previous studies found a higher prevalence of cardiac disease (16%), (22%), and (36%) [23], [39], [40].
In the present study, 21 (13.9%) patients had a significant history of stroke. Similar results were found by Renna et al. and Chatziontantinou et al., who reported that (12.7) and (12.5%) of patients had previous history of stroke, respectively [35], [41]. Other studies found higher occurrence of prior stroke/TIA (18.1%) [29] (21.7%) [30], 38 (2.7%) [24] and (18.6%) [23]
Two (1.3%) patients had eclampsia in our study. Nevertheless, it is crucial to note that preeclampsia/eclampsia serves as a significant risk factor for both ischemic and hemorrhagic strokes in women who have a stroke during pregnancy. In an illustrative case series conducted in France, a total of

31 women who had stroke during pregnancy were examined. Approximately half of the cases (n = 15) were identified as ischemic strokes, with preeclampsia/eclampsia being the cause in 6 instances, accounting for 47% of the cases. Among the individuals who had hemorrhagic strokes, seven individuals, accounting for 44% of the total, were found to have eclampsia, with either HELLP syndrome or disseminated intravascular coagulation [42]. In the context of Taiwan, it was observed that 37% of women who had peripartum stroke, namely 7 out of 19 individuals, had a medical history of hypertensive intracerebral hemorrhage or preeclampsia/eclampsia [43]. The restricted nature of these single-center case series stems from their small sample numbers; nevertheless, larger cohort studies have since validated this link. According to the research conducted on the Nationwide Inpatient Sample data from 2000 to 2001, it was shown that the occurrence of preeclampsia during pregnancy was linked to a fourfold increase in the likelihood of experiencing a stroke (OR 4.4; 95% CI 3.6–5.4) [44].

In our study, arterial fibrillation was reported in 4 (2.6%) of patients, which is similar to Aquilera-Pena et al., and Amaya Pascasio et al., who noted that AF was found in (3.2%) and (3.8%), respectively [21], [45]. At the same time, two studies found lower rates (1.0%) and (1.8%) of patients diagnosed with AF [24], [29].

About two (1.3%) of the patients had migraine in our study. This is nearly similar to Wu et al., who observed (0.5) of patients were migraineurs [46]. On the other hand, Hassan et al., Amaya Pascasio et al., Aguilera-Pena et al., and Nases et al. found higher incidences of migraine in (12.9%), (6.5%), (15.1%), and (17.6%) of patients, respectively [21], [23], [45], [47], [47].

Six (4.0%) patients had Ischemic heart disease, and 1 (0.7%) had coronary heart disease in the current study. One study found similar ischemic heart disease results in (5%) of patients [21]. In one previous study, Coronary artery disease was higher in 4 (5%) patients Patients who have had a stroke or TIA often have coronary artery disease (CAD), which is a major cause of death and disability [48]. While recurrent strokes are more often seen than cardiac events in the long-term aftermath of a stroke, it is important to note that cardiac events still contribute to a higher percentage of death [49], [50].

Postpartum was found in 3 (2.0%) of patients in our study, which is similar to a study reported postpartum in 2 (2.4%) patients [31]. The focus of our case report pertains to an uncommon manifestation of a postpartum ischemic stroke subsequent to a cesarean section procedure. Cheng et al. found that there is an elevated incidence of postpartum stroke during the first year after childbirth. Specifically, 58.4% of stroke cases were seen to transpire within the first 10 days after delivery [51], [52].

The precise etiology of heightened risk during the postpartum period remains uncertain; nevertheless, it is postulated that an elevation in blood pressure within three to five days, attributable to fluid redistribution and compromised cerebral autoregulation, may augment the likelihood of stroke occurrence [53]. Several studies have been conducted to investigate the association between cesarean delivery and the possible risk of ischemic stroke. The link between postpartum stroke and cesarean section and hypertensive disorders of pregnancy has been established in studies conducted by Witlin et al., Lanska, and Kryscio [54], [55].

Myocardial infarction was found in 6 (4.0%) of patients in our study. This is nearly similar to Aguilera-Pena et al., who found that myocardial infarction was present in (2.6%) [45]. At the same time, some studies reported higher history of myocardial infarction in (10.2) and (16.7%) of patients [47], [56].

The current study found atherosclerosis in 13 (8.6%) patients. Three studies observed Atherosclerosis in (6.5%) [57], 10 (12.5%) [58], 2 (6.7) [32]. Although Ge et al., and Chen et al., reported higher incidence of atherosclerosis (43.7) [29], [59].

One (0.7%) of patients had an aneurysm in the current study. This is nearly similar to Wu et al. and Kim et al., who found an aneurysm in (0.5%) and (0.4%) [46], [57]. The occurrence of ischemic symptoms in relation to intracranial aneurysms is infrequent. In our multicenter study, a prevalence rate of 3.3% was observed. The prevalence of the three university hospitals was found to be comparable, despite the use of distinct methodologies for estimating prevalence [60]. Raps et al. [61], In a research conducted on a cohort of 111 individuals with a total of 132 unruptured aneurysms, it was shown that 7 patients (6.3%)

had ischemia symptoms inside a vascular area located distally to the aneurysm. Wiebers et al. [62], the study revealed that a total of 4 out of 130 individuals, accounting for 3.0% of the sample, had embolic events associated with their unruptured aneurysms. Ischemic cerebrovascular illness was found in 11% of patients with unruptured intracranial aneurysms, according to the International Study of Unruptured Intracranial Aneurysms [63]. Unruptured cerebral aneurysms are also a rare finding in the examination of individuals suffering from ischemic strokes. In their study, Nagashima et al. [64] documented a prevalence rate of 5% for unruptured aneurysms among a cohort of 2540 patients diagnosed with ischemic strokes who had undergone cerebral angiography. In a comprehensive multicenter investigation examining cerebral ischemia episodes, it was shown that out of a total of 500 patients, a small proportion of 3 individuals (0.6%) were found to have intracranial aneurysms [65]. MRI was performed on a group of 118 individuals who had symptoms suggesting an ischemic stroke, Qureshi et al. [66] discovered two individuals (1.7% of the total) who had intracranial aneurysms in the vascular tree supplying the infarct area.

Cerebral venous sinuous thrombus was found in 1 (0.7%) of patients in the present study. One study reported higher incidence of venous sinus thrombosis in 6 (1.4%) [46]. Cerebral venous thrombosis (CVT) is an infrequent cerebrovascular disorder with an annual incidence rate of around 5 cases per 1 million individuals, constituting 0.5% of the total stroke cases [67]. Cerebral venous thrombosis results in a diminished flow of blood and cerebrospinal fluid, leading to a notable venous infarct in around half of those afflicted by this condition. In contrast to arterial infarctions, cerebral venous thrombosis (CVT) mostly impacts individuals in the pediatric and young adult age groups. This condition has significant relevance as a leading contributor to stroke occurrences among the younger demographic [68].

In our study, Ehlers-Danlos syndrome in one (0.7%) patient. Ekker et al. found higher rate of Ehlers-Danlos syndrome in 3 (0.2) of patients [34]. Ehlers–Danlos syndrome (EDS) is a collection of conditions characterized by common basic features such as skin hyperextensibility, joint hypermobility, and tissue fragility. This syndrome is seen in an estimated prevalence of roughly 1 in 5000 persons [69]. Out of the six major types of EDS, the most commonly seen are classic (EDS types I and II), hypermobility (EDS type III), and vascular (EDS type IV) [70]. Case reports and smaller studies have linked EDS to a variety of cerebrovascular problems, such as ischemic and/or hemorrhagic strokes, dissections of the brain and neck, and aneurysms of the brain and neck [71], [72].

The current study shows a cortical venous thrombus in 4 (2.6%) patients. ICVT accounts for fewer than 1% of all ischemic strokes and causes only 6.3% of cerebral venous and sinus thrombosis. The average age of patients upon diagnosis was found to be 41, and of those diagnosed, 68% are female, according to an examination of 47 case reports/case series [73]. On average, individuals diagnosed with cortical vein thrombosis, isolated cortical vein thrombosis, and cerebral venous thrombosis tend to be younger compared to those identified with arterial strokes. Females are also more susceptible to elevated risk levels compared to males [74].

Aortic stenosis was observed in one (0.7%) in the current study. A previous study discovered that Ischemic stroke in one patient is likely due to a heart defect that causes brain ischemia due to decreased cardiac output so that blood flow in the brain reduced and possibly due to embolism due to aortic stenosis causing flow stasis blood, thereby facilitating the formation of thrombus and emboli [75].

Our study found heart failure in 9 (6.0%) patients, higher than previously published studies. They observed that heart failure was found in (1.3%) [35] (0.7%) [29], (1.1%) [21], (3.9%) [45] 4 (0.3%) [24] of patients.

PFO was found in 7 (4.6%) patients in the current study. Two previous studies reported nearly similar results in patent foramen ovale in (2.6%) and (5.9%) [37], [45] Amaya Pascasio et al. and Chatzikonstantinou et al. found higher rate of PFO in (10.3%), and (27.9%) of patients [21], [41].

Cerebral venous sinuous thrombus 1 (0.7%) in the current study. The frequency of cerebral venous sinus thrombosis (CVST) varies widely across research. Two to five new instances of CVST per million people are diagnosed each year [67], [76]; however, it is probable that the true magnitude of the phenomenon is

underestimated due to the dearth of well-conducted epidemiological investigations. Two new studies conducted in the Netherlands and southern Australia have shown a higher prevalence of yearly cases, namely 13.2 and 15.7 instances per million, respectively, which exceeds the previously reported figures [77], [78]. The elevated occurrence of infection-related cerebral venous sinus thrombosis (CVST) may lead to even more pronounced rates in some nations, such as Pakistan, where it reaches 18%. However, the precise frequency of CVST among distinct ethnic populations has to be determined and is now under research [79]–[81]. In contrast to the higher incidence of arterial stroke seen in older individuals, cerebral venous sinus thrombosis (CVST) mostly affects young people, with an average age of 35 years. Furthermore, this condition is more often diagnosed in women than in males, with a ratio of 2.2 to 1, due to the presence of sex-specific risk factors [82]. Sixty percent of patients will have involvement in the superior sagittal and transverse sinuses, while twenty percent will have involvement in the internal jugular or cortical veins. More than one sinus is affected by CVST in almost two-thirds of patients [83].

Conclusion

The findings of this study indicate that the most prevalent risk factors for ischemic stroke among young people in the local area include hypertension, diabetes mellitus, cardiac diseases, and smoking.

Ethical approval

This prospective study was approved by the Advance Studies and Research Board (ASRB), University of Sindh, Jamshoro, Sindh, Pakistan. **Registration No. DRGS/2421**

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Declaration of competing interest

None

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