

Prevalence of risk factors of ischemic stroke in a local Pakistani population

High-density lipoproteins, an emerging risk factor

Zeeshan Basharat, Medical Student, **Sadaf Mumtaz**, MBBS, PhD (UK), **Farah Rashid**, MBBS, MPH, **Sanah Rashid**, Medical Student, **Sumaiya A. Mallam**, Medical Student, **Asghar Diljan**, Medical Student, **Neil Iftikhar-Maken**, Medical Student, **Safa Zafar**, Medical Student, **Irum Rehman**, MBBS (Pb).

ABSTRACT

الأهداف: التحقق من نسبة انتشار عوامل الخطر التي تزيد من خطر الإصابة بالسكتة الدماغية الإقفارية بين المرضى الباكستانيين.

الطريقة: شملت هذه الدراسة الاستراتيجية المقطعية المرضى الذين ثبتت إصابتهم بالسكتة الدماغية الإقفارية من خلال الأشعة المقطعية منذ عامين خلال الفترة من يناير 2007م إلى ديسمبر 2009م، والذين أدخلوا إلى قسم الأعصاب، مستشفى شيفا العالمي، إسلام آباد، باكستان. لقد كان المرضى من كلي الجنسين وبدون حدود عمرية. لقد قمنا بتحليل البيانات من خلال تقسيم المرضى إلى 3 مجموعات على حسب العمر وذلك اعتماداً على نسبة انتشار عوامل الخطر وهذه المجموعات كالتالي: مجموعة 1 (25-55) (23.8%)، ومجموعة 2 (56-71) (43.4%)، ومجموعة 3 (72-103) (32.7%).

النتائج: شملت الدراسة 418 من المرضى، وقد استثنينا 137 مريض من الدراسة نظراً لعدم توفر معلومات كافية. وهكذا قمنا بتحليل البيانات الخاصة بحوالي 281 مريضاً. لقد كان متوسط عمر المرضى 65 ± 0.8 عاماً، وكانت نسبة الذكور إلى الإناث 1.30:1. ولقد كانت أكثر عوامل الخطر التي تزيد من خطر الإصابة بالسكتة الدماغية الإقفارية كالتالي: ارتفاع ضغط الدم (86.8%)، تلاه مرض السكري (59.8%)، واختلال مستوى الدهون البروتينية (59.1%)، والتدخين (18.1%). ولقد كانت نسبة انتشار عوامل الخطر الأربعة بين المجموعة 56-71 هي الأكثر مقارنة بالمجموعتين الأخرتين. وعندما قمنا باعتبار الجنس فقد كانت نسبة انتشار ارتفاع ضغط الدم، واختلال مستوى الدهون البروتينية مرتفعه لدى المجموعة 1. وكانت مستويات الكوليسترول مرتفع الكثافة هي أكثر الدهون ارتفاعاً وخصوصاً في المجموعة 1، وكان ذلك يعرضهم لخطر السكتة الدماغية أكثر من غيرهم.

خاتمة: أظهرت هذه الدراسة بأن تقليل مستويات الكوليسترول مرتفع الكثافة، والتحكم بضغط الدم يعد ضرورياً من أجل تقليل خطر الإصابة بالسكتة الدماغية وخصوصاً في المراحل المبكرة (≤ 25)، كما يمكن اعتبار مثل هذه العوامل من الدلائل المفيدة لتحديد المرضى المعرضين أكثر من غيرهم لخطر الإصابة بالسكتة.

Objective: To ascertain the prevalence of risk factors for ischemic stroke in Pakistani patients at Shifa International Hospital (SIH), Islamabad, Pakistan.

Methods: This retrospective cross-sectional study included patients of either gender, with no age limit admitted to the Department of Neurology at Shifa International Hospital, Islamabad, Pakistan, with the diagnosis of stroke verified by brain CT scan during a period of 2 years from January 2007 to December 2009. The data were analyzed by grouping our patients according to their age based on the frequency of risk factors. Group 1; 25-55 years (23.8%), group 2; 56-71 years (43.4%), and group 3; 72-103 years (32.7%).

Results: A total of 418 patients were included in the study; 137 patients were excluded due to incomplete information. The data from the remaining 281 were analyzed. The mean age of the population was 65 ± 0.8 years, and the male to female ratio was 1.30:1. The most frequent risk factors included hypertension 86.8% followed by diabetes mellitus 59.8%, dyslipidemia 59.1%, and smoking 18.1%. The highest frequency of 4 risk factors was present in the age group 56-71. Gender distribution of risk factors showed that hypertension and dyslipidemia are major risk factors in group 1. Abnormal high-density lipoproteins (HDL) emerged as the major lipid among 3 groups, especially in group 1, which predisposed to stroke.

Conclusion: A decrease in HDL and control of blood pressure is important to reduce the risk of stroke especially in early age (namely, ≥ 25 years) and could become an increasingly useful tool to identify patients at a high risk of stroke.

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From the Sections of Physiology (Mumtaz, Rehman) and Community Medicine (Rashid), Shifa College of Medicine (Basharat, Rashid S, Mallam, Diljan, Iftikhar-Maken, Zafar), Shifa International Hospital, Islamabad, Pakistan.

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Address correspondence and reprint request to: Dr. Sadaf Mumtaz, Assistant Professor of Physiology, Section of Physiology, Shifa College of Medicine, Shifa International Hospital, Pitras Bukhari Road, Sec H-8/4, Islamabad 44000, Pakistan. Tel. +92 (51) 8463365. Fax. +92 (51) 4435046. E-mail: dr_sadaf_mumtaz@yahoo.com / sadaf.mumtaz@shifacollege.edu

Globally, each year 15 million people experience stroke. From these, 5 million die and another 5 million are left permanently disabled. This has a huge impact on the individual families and community, particularly in the underdeveloped world.¹ Stroke is a clinical syndrome represented by quickly developing symptoms and/or signs of focal, and at times global (for patients in coma), loss of cerebral functions, with no obvious cause other than that of vascular origin with symptoms lasting more than 24 hours or leading to death.² However, transient ischemic attacks (TIA) last less than 24 hours, and patients with stroke symptoms caused by subdural hemorrhage, tumors, poisoning, or trauma are excluded.³ According to a World Health Organization (WHO) report from 2002,⁴ the total mortality from stroke in Pakistan is more than 75,000. The risk factors for stroke are classified as non-modifiable and modifiable. Non-modifiable risk factors include age, family history, prior stroke, gender, and race, whereas modifiable risk factors are hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, dyslipidemia, cigarette smoking, obesity, valvular heart disease, homocystinemia, alcohol abuse, and physical inactivity.⁵

According to the WHO estimates for the year 2020, stroke will remain the second leading cause of death along with ischemic heart disease both in developing and developed countries.⁶ Data on stroke incidence and prevalence from Pakistan is scarce. Albeit, there are studies suggesting significant differences in terms of stroke epidemiology, risk factors, and stroke subtypes.^{1,3,6,7} A handful of Pakistani hospital based studies, in settings using advanced investigative approaches such as CT-scan, have revealed 31-40% cases of stroke due to cerebral hemorrhage, and 60-90% due to ischemia.^{1,7} Due to the high mortality rate and the limitation of treatment on prognosis found in patients with cerebral stroke, it is time to act and identify the risk factors for stroke in the local Pakistani population. No doubt, the potential to reduce or limit the cases relies on primary prevention. This implies reliable information in our settings on the factors related to the risk of stroke.

Therefore, the purpose of this study was to provide information regarding prevalence of the major modifiable risk factors (namely, hypertension, diabetes mellitus, smoking and dyslipidemia) among the stroke patients presenting to Shifa International Hospital,

which receives patients not only from major cities like Islamabad and Rawalpindi, but also from its vicinity. We concentrated on ischemic stroke due to its high prevalence compared to hemorrhagic stroke reported in several Pakistani studies, and possible positive association of ischemic stroke with serum cholesterol.

Methods. This is a retrospective cross-sectional study conducted in the Department of Neurology at Shifa International Hospital, Islamabad, Pakistan. This research was conducted after obtaining approval from the Institutional review board and ethical committee of Shifa International Hospital, and according to the principles of the Helsinki Declaration. The Shifa International Hospital database was searched for all patients enrolled in the services of the Neurology Department from January 2007 to December 2009. Clinical information written at the time of admission was abstracted. During 2007 to 2009, 418 patients were discharged with the primary diagnosis of stroke. From these 418, 137 patients were excluded due to incomplete information. Data from the remaining 281 were analyzed using standardized performa. The following parameters were recorded: Age, gender, and previous history of hypertension, diabetes, smoking, and dyslipidemia. Charts of patients who had no previous history of any of the primary risk factors were also reviewed. All patients recruited to the study had a history of acute onset neurological deficit (either focal or global), which lasted more than 24 hours, and underwent brain CT at the time of admission to rule out hemorrhage.

Hypertension was defined as blood pressure >140/95 mm Hg on 2 separate occasions, or the use of antihypertensive medication at any time before the onset of stroke.⁸ Patients were diagnosed as diabetic if fasting plasma glucose level was >126 mg/dl on more than one occasion, or random glucose level >200 mg/dl on more than one occasion.⁹ Patients who were normoglycemic at the time of presentation, but with a history of diabetes, taking insulin, or oral hypoglycemics were also labeled as diabetics. Hyperlipidemia was defined as cholesterol in excess of 200 mg/dl, triglycerides of more than 200 mg/dl, low-density lipoproteins (LDL) of more than 130 mg/dl, and HDL of less than 40 mg/dl in men and 50 mg/dl in women.^{7,10} A smoker was defined as a person who smoked at least one cigarette per day for the preceding 3 months or more, or had tobacco use in any form.¹¹

A detailed history of patients with special emphasis on predisposing illnesses such as hypertension, diabetes mellitus, hyperlipidemia, and smoking was taken

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Table 1 - Frequency distribution of stroke risk factors in male and female Pakistani patients.

Age groups (years)	Hypertension				Diabetes				Smoking				Dyslipidemia			
	Male	Female	Total	(%)	Male	Female	Total	(%)	Male	Female	Total	(%)	Male	Female	Total	(%)
Group 1 (25-55)	23	22	45	(73.7)	14	18	32	(52.4)	5	0	5	(8.1)	23	22	45	(73.7)
Group 2 (56-71)	70	45	115	(89.8)	53	31	84	(65.6)	28	1	29	(22.6)	49	27	76	(59.3)
Group 3 (72-103)	46	37	83	(91.2)	28	24	52	(57.1)	14	3	17	(18.6)	27	17	44	(48.3)

into account. General physical, detailed neurological examination, and laboratory investigations were analyzed. Patients with first stroke and presenting within 24 hours after stroke were included in this study. Patients with recurrent strokes were also included, however, only their first stroke was taken into account. Patients who had the diagnosis of hemorrhagic stroke were excluded.

We analyzed our data comprehensively by grouping our patients according to their age. This grouping was based on the highest frequency of risk factors seen in patients of age (years) ranging from 56-71. Group 1 included patients with age (years) ranging from 25-55 (23.8%), group 2 from 56-71 (43.4%), and group 3 from 72-103 (32.7%). We used the Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA) to analyze the data from 281 patients. Quantitative variables were expressed as mean \pm SEM. Qualitative variables were analyzed by finding their frequencies or percentages. Groups were compared using one-way ANOVA, where appropriate significance was assumed for p -values <0.05 .

Results. A total of 281 patients met the inclusion criteria and were selected for the study. The age range was from 25-103, with a mean age of 65 ± 0.8 years. There were 159 (56.6%) males and 122 (43.4%) females, with a male to female ratio of 1.30:1. Of 122 females, 101 were of postmenopausal age. The distribution of risk factors was as follows: hypertension 244 (86.8%), the most commonly found risk factor followed by diabetes mellitus 168 (59.8%), dyslipidemia 165 (58.7%), and smoking 51 (18.1%). Most of the cases had prevalence of more than one risk factor of stroke.

Frequencies of risk factors of stroke on the basis of age and gender. The frequencies of risk factors of stroke according to age, gender, and total percentages in the 3 different groups are shown in Table 1. Groups 2 and 3 had the highest percentage of hypertensive patients, however, a significant difference was observed between group 1, 2, and group 3 ($p=0.02$). A significant

difference among diabetics was seen in group 1 and 2 ($p=0.004$). The most significant risk factors in group 1 were dyslipidemia and hypertension when compared with group 2 and 3 ($p=0.002$). With dyslipidemia, a significant difference was observed between groups 1, 2, and 3 ($p=0.002$).

Gender distribution of risk factors provided a very interesting insight in our local Pakistani hospital based study. In both genders, the prevalence of risk factors of stroke increased markedly with advancing age. Hypertension and dyslipidemia are major risk factors in both genders of group 1, as shown in Table 2 and Figure 1. With advancing age, as seen in groups 2 and 3, hypertension takes a leading edge, and is a major risk factor in both males and females followed by diabetes, dyslipidemia, and smoking (Table 2 & Figure 1).

Dyslipidemia - an emerging risk factor. Although the role of blood lipids in coronary artery disease is well known, the role of lipids is now emerging as one of the major risk factors of stroke. It is especially intriguing to see the occurrence of stroke in group 1 in both males and females with the major risk factors of dyslipidemia and hypertension shown in Table 2. Although hypertension is the major risk factor in the 3 defined groups, targeting individuals with abnormal lipids at an early age (namely, group 1) can limit the number of patients of stroke.

The gender distribution with abnormal lipids in Table 3 clearly demonstrates the vulnerability of group 1. Seventy-nine percent of males and 68% females in group 1 were exposed to abnormal lipids

Table 2 - Percentages of stroke risk factors in male and female Pakistani patients.

Age groups (years)	Hypertension		Diabetes		Dyslipidemia		Smoking	
	Male	Female	Male	Female	Male	Female	Male	Female
Group 1 (25-55)	79.3	68.7	48.2	56.2	79.3	68.7	17.2	0.0
Group 2 (56-71)	89.7	90.0	67.9	62.0	62.8	54.0	35.8	2.0
Group 3 (72-103)	88.4	94.8	53.8	61.5	51.9	43.5	26.9	7.6

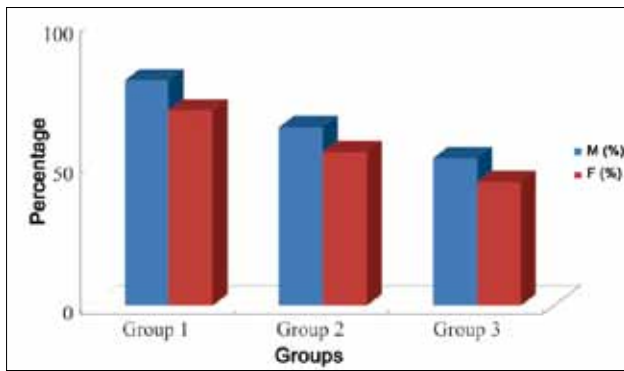


Figure 1 - Percentages of males and females with dyslipidemia in Pakistani stroke patients.

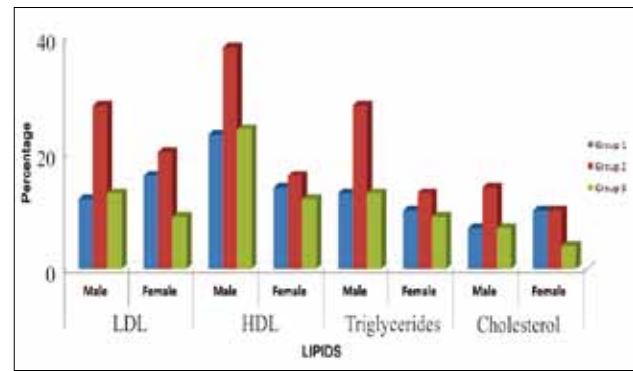


Figure 2 - Gender based percentages of low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and cholesterol in Pakistani stroke patients.

(Figure 1). We screened the lipid profile of our sample due to the high prevalence of stroke in individuals with dyslipidemia, especially in group 1. Our results show that an abnormal HDL level is the major lipid among the 3 groups, which is predisposing to stroke (Table 3 and Figure 2). In males, abnormally high levels of LDL, HDL, triglycerides, and cholesterol were seen in the 3 groups (Figure 2). However, an abnormal HDL level in group 2 in males is an important finding. In contrast, in females a mixed pattern was observed with LDL, HDL, triglycerides, and cholesterol in the 3 groups. However, an abnormal LDL level in group 2 in females is a novel finding (Figure 2).

The results in our study using one-way ANOVA clearly show that hypertension ($p=0.003$) and dyslipidemia ($p=0.007$) are the emerging risk factors in an Asian Pakistani population followed by diabetes ($p=0.02$) and smoking $p=0.05$.

Discussion. Stroke is a major cause of morbidity and mortality with disability and social dependence surpassed only by heart disease and malignancies.¹²⁻¹⁵ According to the WHO DALY's (disability adjusted life years) report 2003¹³ on stroke, the number of years

lost due to ill-health, disability, or early death per 1000 population of standardized age is 5-9 years for Pakistan, and 10-14 for India. The main pathological types of stroke are cerebral infarction, primary intra-cerebral and subarachnoid hemorrhage.^{6,14} The risk of death depends on the type of stroke. Transient ischemic attack (TIA) has the best outcome followed by stroke caused by carotid stenosis. The blockage of any artery with rupture of a cerebral blood vessel is the most dangerous of all.⁶

In the present study, we explored the prevalence of risk factors for ischemic stroke due to its high incidence in the Pakistani Asian population. We found hypertension to be the major risk factor for this study (Table 1). Similar findings were reported in other hospital based Pakistani studies,^{5,14,16-20} with the following percentages, 61%, 59%, 62%, 58%, 70%, and 56.4%. However, in the present study in group 1 (25-55 years), dyslipidemia contributed equally to stroke occurrence (Table 1), and this is a novel finding. The higher prevalence of dyslipidemia in group 1 could be due to stress, smoking, and underlying diabetes.

A 12-month follow up of the Fukuoka stroke registry²¹ showed that low levels of HDL cholesterol are considered

Table 3 - Gender based frequency distribution of low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and cholesterol in Pakistani stroke patients.

Age groups (years)	Low-density lipoproteins				High-density lipoproteins				Triglycerides				Dyslipidemia			
	Male	Female	Total	(%)	Male	Female	Total	(%)	Male	Female	Total	(%)	Male	Female	Total	(%)
Group 1 (25-55)	12	16	28	(57.1)	23	14	37	(75.5)	13	10	23	(47.9)	7	10	17	(34.6)
Group 2 (56-71)	28	20	48	(53.9)	38	16	54	(61.3)	28	13	41	(46.0)	14	10	24	(27.3)
Group 3 (72-103)	13	9	22	(40.7)	24	12	36	(66.6)	13	9	22	(41.5)	7	4	11	(20.3)

independent risk factors for recurrence of ischemic stroke. In our study, abnormal HDL levels among the 3 groups was the most important finding followed by LDL, triglycerides, and cholesterol. Albeit in females abnormally high LDL was an intriguing contributory factor when compared to HDL, triglycerides, and cholesterol (Table 3 & Figure 2). Pedro-Botet et al,²² in 1992 stated that increased serum lipoprotein levels and intermediate density lipoprotein abnormalities together with decreased high-density lipoprotein levels are major risk factors for ischemic cerebrovascular disease, even in normocholesterolemic and normotriglyceridemic subjects.²² Another study indicated that pretreatment with statins, either in hypercholesterolemia, or in ischemic stroke patients could have neuroprotective effects with reduced neurological deficits at presentation, lower early death and dependency rate, thus increasing the chances for good outcome.²³ A recent study conducted in rural china reported raised LDL in both men and women, and triglyceride to HDL ratio levels were related to increased risks of ischemic stroke in women; findings very similar to our study.²⁴ We suggest that identifying abnormal HDL and LDL levels in due time can have a beneficial role in the prevention and prognosis of stroke.

Diabetes mellitus has reached epidemic proportions in the Pakistani population.^{6,25} It increases the risk of stroke several folds. The number of patients with impaired fasting glucose and impaired glucose tolerance is very high.^{26,27} In this study, 59.8% of patients were diabetic, and our values are higher than those reported in previous studies.^{14,17-20,26} Previous studies comparing Pakistanis with Bangladeshis, Indians, and Caucasians have shown that Pakistanis have a higher BMI and a more sedentary life style, which has direct effects on glucose metabolism.²⁸ This suggests diabetes as an important risk factor in our population.

Cigarette smoking is a potent risk factor for ischemic stroke.^{29,30} In this study, 18.1% of the patients were smokers (predominantly males). Twenty-three percent of smokers were found in group 2, and 19% in group 3 (Table 1). These percentages are lower than those obtained in previously conducted studies.^{14,17,20} The reason for obtaining lower percentages is due to social pressures faced by individuals, especially females. Cigarette smoking is associated with a 19% higher mortality from stroke.³ The numbers of reported cases are significant where the rate of smoking is often negligible in women.

We carried out a cross-sectional study representing a subset of the population, however, larger multicenter studies are required to identify the true incidence and

prevalence of risk factors of stroke to reduce the burden of this disease in Pakistan.

Proposal for action. There is a need to raise awareness in the population regarding lifestyle changes and early identification of the major modifiable risk factors. Large multicentre nationwide population based prevalence, and incidence studies are required. Physicians should identify risk groups and encourage them toward good compliance to drugs and proper disease control. We need to develop proper prevention and treatment guidelines specific to our population and region.

In summary, this study shows that dyslipidemia and hypertension are the emerging risk factors in early age (namely, ≥ 25 years) in our population. This needs attention and screening for early diagnosis to reduce the number of cases of stroke at later stages (namely, ≥ 50 years) of life to reduce the burden of this disease in our settings.

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