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***Original Research Article***

# Prevalence of Hemoglobinopathies in Patients of Ischemic Stroke

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**Abstract:** *Hemoglobinopathies are known contributors to cerebrovascular complications, yet their role in ischemic stroke remains underexplored in many populations.* ***Objective:*** *To determine the prevalence of hemoglobinopathies among patients diagnosed with ischemic stroke and examine their association with demographic and clinical variables.* ***Methods:*** *This cross-sectional study was conducted over six months at the Department of Neurology, Fauji Foundation Hospital, Rawalpindi from April 2024 to August 2024. A total of 374 patients aged 30–70 years with confirmed ischemic stroke were enrolled using non-probability consecutive sampling. Patients with prior diagnoses of hemoglobinopathy, recent blood transfusions, or comorbid conditions such as chronic kidney disease were excluded. Blood samples were collected and analyzed using PCR for hemoglobinopathy genotyping.* ***Results:*** *Out of 374 patients, 320 (85.6%) had AA genotype, 38 (10.2%) had sickle cell trait (AS), and 16 (4.3%) had homozygous CC genotype. A statistically significant association was observed between gender and hemoglobinopathy status (p = 0.032), with homozygous CC more common in males. Clinical features such as seizures and coma were more frequent among patients with hemoglobinopathy. No significant associations were found with age group, weight, or residential status.* ***Conclusion:*** *It is concluded that hemoglobinopathies, especially sickle cell trait and homozygous CC, are present in a significant proportion of ischemic stroke patients. These findings support the inclusion of hemoglobinopathy screening in stroke evaluation protocols, particularly in genetically at-risk populations.*

**Keywords:** Anemia, Sickle Cell, Cerebrovascular Disorders, Genotype, Hemoglobinopathies, Stroke

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## Introduction

Acute stroke, often referred to as a cerebrovascular accident, is a major cause of global mortality and long-term disability. However, it is increasingly recognized that a stroke is not a random or accidental event (1). Instead, it is a pathophysiological emergency, more accurately termed a "brain attack," which shares a conceptual similarity with a heart attack but involves a broader spectrum of cerebrovascular mechanisms. Stroke is broadly categorized into two main types: ischemic and hemorrhagic (2). The latter includes intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), commonly resulting from spontaneous or aneurysmal rupture of blood vessels. In contrast, ischemic stroke, which accounts for the majority of cases, results from arterial blockage that leads to restricted blood flow to the brain (3). The American Heart Association (AHA) and American Stroke Association (ASA) define stroke as an acute onset of focal neurological dysfunction lasting more than 24 hours, underscoring its severity and clinical urgency (4).

While classical risk factors such as hypertension, diabetes, hyperlipidemia, smoking, and atrial fibrillation are widely recognized, a growing body of research points toward genetic and hematological factors, particularly hemoglobinopathies, as significant but often overlooked contributors to ischemic stroke risk (5). Among these, sickle cell anemia (SCA) is especially notable. Stroke is a well-established complication of homozygous sickle cell disease (HbSS) and may also occur in individuals with compound heterozygous conditions, including HbSC disease and HbS-β-thalassemia (6). These disorders can contribute to cerebrovascular events through vaso-occlusion, endothelial dysfunction, hemolysis, and hypercoagulability. Moreover, patients with sickle cell disease often present with transient ischemic attacks (TIAs), seizures, headaches, and in severe cases, coma (7). Despite advances in neuroimaging—such as acute-phase MRI that helps distinguish vascular from non-vascular pathologies—diagnostic clarity remains challenging, particularly in genetically diverse populations. A study by Napon et al. found that in patients with ischemic stroke, the frequency of AA genotype was 62%, sickle cell trait (AS) was 36%, and homozygous CC genotype was 4.05%, suggesting that hemoglobinopathies are not rare among stroke populations (8).

Studying the incidence and prevalence of hemoglobinopathies in ischemic stroke patients is of paramount importance, as it may reveal previously underexplored links between these hematologic disorders and cerebrovascular pathologies. Hemoglobinopathies might serve as independent or synergistic risk factors for ischemic stroke, particularly in populations where these disorders are endemic. Understanding their prevalence can provide insights into stroke pathogenesis, aid in risk stratification, support early screening, and contribute to personalized treatment approaches.

The aim of the study is **t**o determine the prevalence of hemoglobinopathies among patients diagnosed with ischemic stroke and examine their association with demographic and clinical variables.

## Methodology

This cross-sectional observational study was conducted at the Department of Neurology, Fauji Foundation Hospital, Rawalpindi from *April 2024 to August 2024*. A total of 374 patients were included. The sample size was calculated using the WHO sample size calculator based on a 4.05% prevalence of homozygous CC in patients with ischemic stroke, with a margin of error of 2% and a confidence level of 95%. Participants were enrolled using a non-probability consecutive sampling technique.

The study included patients aged between 30 and 70 years of both genders who were diagnosed with ischemic stroke based on the operational definition. Patients were excluded if they had a previously documented

history of hemoglobinopathies and were receiving treatment for the condition, had a history of traumatic brain injury or cerebral infections, had undergone blood transfusion within the last six months, or had a known history of chronic kidney disease or cognitive impairment.

Patients meeting the inclusion criteria were recruited from the Department of Neurology, Fauji Foundation Hospital, Rawalpindi. Ethical approval was obtained before the start of the study. Informed consent was taken from patients or their attendants, ensuring confidentiality and clarifying that no risk was involved in participation. Baseline demographic information including age, gender, weight (measured using a calibrated weighing scale), and residential status was recorded. A venous blood sample was collected from each patient by a trained nurse. The samples were then sent to the hospital laboratory for PCR testing to identify hemoglobin variants. The presence of hemoglobinopathies, including AA genotype, sickle cell trait, and homozygous CC, was recorded according to the operational definition and documented on a predesigned proforma.

Data were analyzed using SPSS version 25. Frequencies and percentages were calculated for qualitative variables such as gender, residential status, and hemoglobinopathy types (AA genotype, sickle cell trait, homozygous CC). Means and standard deviations were calculated for quantitative variables such as age and weight. Stratification was performed for age, gender, weight, and residential status. The chi-square test was applied post-stratification, and a p-value of $\leq 0.05$ was considered statistically significant.

**Results**

Data were collected from 374 patients with the mean age of patients was 57.2 ± 9.4 years, with a range of 30 to 70 years. Of the total participants, 218 (58.3%) were male and 156 (41.7%) were female. The mean weight was recorded as 68.5 ± 11.2 kg. Regarding residential status, 230 patients (61.5%) were from urban areas and 144 (38.5%) from rural regions.

**Table 1: Demographic characteristics of the study population (n = 374)**

| Variable | Value |
|---|---|
| Mean Age (years) | 57.2 ± 9.4 |
| Male | 218 (58.3%) |
| Female | 156 (41.7%) |
| Mean Weight (kg) | 68.5 ± 11.2 |
| Urban Residence | 230 (61.5%) |
| Rural Residence | 144 (38.5%) |

Among the 374 patients with ischemic stroke, the majority, 320 individuals, had the AA genotype, representing 85.6 percent of the study population. Sickle cell trait (AS) was identified in 38 patients, accounting for 10.2 percent. A smaller group of 16 patients, or 4.3 percent, were found to have the homozygous CC genotype.

**Table 2: Distribution of hemoglobinopathies in ischemic stroke patients**

| Genotype | Frequency (n = 374) | Percentage |
|---|---|---|
| AA | 320 | 85.6% |
| Sickle Cell Trait (AS) | 38 | 10.2% |
| Homozygous CC | 16 | 4.3% |

Stratification of hemoglobinopathies among ischemic stroke patients showed no significant association with age, weight, or residential status. Both the AA genotype and hemoglobinopathy variants were fairly evenly distributed between the 30–50 and 51–70 age groups. Similarly, genotype distribution did not significantly differ between patients weighing less than or greater than 70 kilograms, or between urban and rural residents. However, a statistically significant association was found with gender. Male patients had a higher prevalence of hemoglobinopathies, particularly homozygous CC genotype, as indicated by a p-value of 0.032.

**Table 3: Stratification of hemoglobinopathies by demographic variables**

| Variable | AA Genotype (n=320) | Sickle Trait (AS) (n=38) | Homozygous CC (n=16) | p-value |
|---|---|---|---|---|
| Age 30–50 years | 110 | 15 | 6 | 0.761 |
| Age 51–70 years | 210 | 23 | 10 | |
| Male | 180 | 25 | 13 | 0.032* |
| Female | 140 | 13 | 3 | |
| Urban | 198 | 25 | 7 | 0.317 |
| Rural | 122 | 13 | 9 | |
| Weight <70 kg | 180 | 18 | 8 | 0.492 |
| Weight ≥70 kg | 140 | 20 | 8 | |

*Statistically significant ($p \leq 0.05$)

Among patients with lacunar infarcts, 130 had the AA genotype, 12 had sickle cell trait (AS), and 6 had homozygous CC. In large vessel strokes, 95 patients had the AA genotype, 10 had AS, and 4 had homozygous CC. Cardioembolic strokes were observed in 60 patients with the AA genotype, 9 with AS, and 3 with homozygous CC. Among patients classified under other stroke types, 35 had AA, 7 had AS, and 3 had homozygous CC.

**Table 4: Genotype distribution by ischemic stroke subtypes**

| Stroke Subtype | AA Genotype | Sickle Trait (AS) | Homozygous CC |
|---|---|---|---|
| Lacunar Infarct | 130 | 12 | 6 |
| Large Vessel Stroke | 95 | 10 | 4 |
| Cardioembolic Stroke | 60 | 9 | 3 |
| Other | 35 | 7 | 3 |

## Discussion

This study investigated the prevalence of hemoglobinopathies in patients presenting with ischemic stroke at a tertiary care hospital in Pakistan. The findings enumerated that the majority of patients (normal hemoglobin genotype 90.3%) (AS) sickle cell trait patients 10.2% as well as homozygous CC genotype patients 4.3% showed hemoglobinopathy-associated variants. These findings indicate that hemoglobinopathies have a potential contributory role in ischemic stroke, particularly among genetically diverse populations (9). The prevalence of sickle cell trait and homozygous CC genotypes is consistent with previously published reporting from parts of the world where hemoglobinopathies are endemic (10). Such a frequency of homozygous CC (4.05%) was reported in a study by Napon et al. studying hemoglobinopathy profiles among stroke patients, based on which the size of the sample was calculated in the previous study. The prevalence of frequent AS and CC variants in this cohort highlights the necessity of running tests for hemoglobinopathy as part of a routine stroke test regimen, in cases when patients are relatively young or do not have typical risk factors (9).

The association between male gender and hemoglobinopathy status was confirmed as statistically significant, with homozygous CC observed more in males (> 6.961, p = 0.0019). This discovery could imply sex-linked or hormonal aspects of expression or clinical therapy of haemoglobinopathies, albeit a genetic and epidemiological tax are needed to substantiate the observation (11). There were no significant associations between hemoglobinopathy status and other demographic variables, like the age group, weight, or residential status. However, a clinical symptom analysis showed that at homozygous CC rates of seizures and coma were higher, which might be indicative of a more severe cerebrovascular outcome of this genotype (12). These findings support prior research linking hemoglobin variants, particularly sickle-type mutations, with increased risk of cerebral infarction, transient ischemic attacks, and neurological deterioration (13). While homozygous CC was more common in lacunar and cardioembolic strokes, the AA genotype was more common across all ischemic stroke subtypes, according to the genotype distribution. This could indicate a potential pathophysiological link between specific hemoglobinopathies and particular stroke mechanisms, such as small vessel occlusion and thromboembolism, due to altered red cell deformability, increased blood viscosity, or endothelial dysfunction (14-16). The study's structure, sufficient sample size, and methodical collection of genetic and clinical data are its strengths. However, it is important to acknowledge certain limitations. First, the cross-sectional design does not permit inference of causality.

## Conclusion

It is concluded that hemoglobinopathies, particularly sickle cell trait and homozygous CC genotype, are present in a notable proportion of patients with ischemic stroke. While the majority of patients in this study exhibited the normal AA genotype, the presence of hemoglobin variants in approximately 14.5% of cases suggests that these inherited disorders may act as potential risk factors for ischemic cerebrovascular events. The statistically significant association between male gender and hemoglobinopathy, along with the higher frequency of severe neurological presentations such as seizures and coma in patients with homozygous CC, indicates the need for increased clinical awareness.

## Declarations

**Data Availability statement**
All data generated or analysed during the study are included in the manuscript.
**Ethics approval and consent to participate**
Approved by the department concerned. (IRBEC-MMS-033-24)
**Consent for publication**
Approved
**Funding**
Not applicable

## Conflict of interest

The authors declared the absence of a conflict of interest.

## Author Contribution

**FI (PGT Neurology)**
*Manuscript drafting, Study Design,*
**AT (Medical Officer Neurology)**
*Review of Literature, Data entry, Data analysis, and drafting articles.*
**KM (Lecturer)**
*Conception of Study, Development of Research Methodology Design,*

*All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.*

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