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# Relationship between Haematological Parameters and Cerebral Blood Flow Velocities in Sickle Cell Anaemia Children Seen At A Tertiary Hospital In Imo State

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**Abstract**

**Background:** Sickle Cell Anaemia (SCA) is a chronic haemolytic state associated with recurrent blood transfusions, infections and its attendant complications. Cerebral blood flow velocities and haematological parameters are used routinely to monitor these children both in steady state and crises. The study compared the relationship between cerebral artery blood flow velocities (CBFV), steady state packed cell volume and white blood cell counts of male and female SCA children aged 2-16 years seen at Federal Teaching Hospital Owerri, Imo state.

**Methods**: Transcranial Doppler ultrasound, haematology test(Packed cell volume and white blood cell count) were done for SCA children that attended the sickle cell specialist clinic of the hospital between April and September 2023.

**Results:** A total of 102 subjects were screened within the study period. The mean packed cell volume was statistically significantly lower in males than females (p= 0.010). There was no difference in the mean white cell count in both genders. Abnormal CBFV was found in17.6% of subjects

**Conclusion:** The prevalence of abnormal cerebral blood flow velocity in SCA children is 17.6%. Identification of subjects at risk for a CVA helped in primary prevention by prompt therapy institution.

**Keywords:** Sickle cell anaemia, cerebral artery blood flow velocities packed cell volume, white blood cell count.

## Introduction

The most common genetic haematological disorder in the world, sickle cell disease (SCD) is caused by a point mutation in the beta chain that replaces hydrophilic glutamic acid with hydrophobic valine.[1] SCD affects 20–25 million people worldwide, with 75% of them living in Africa, particularly in malaria-endemic

areas like Nigeria, Senegal, Madagascar, etc.[2] SCA affects up to 2% of the world's population, with 90% of those affected living in Nigeria, India, and the Democratic Republic of the Congo.[4]

Cerebrovascular accidents (CVAs) can cause devastating and potentially fatal strokes. The neurologic complications of SCA are among the most severe, affecting almost every system of the body and occurring in at least 25% of affected patients [5,6,7]. These neurologic complications include ischaemic and hemorrhagic strokes, transient ischaemic attacks, silent cerebral infarction, seizures, headaches, and visual loss [8,9,10]. CVA may be silent, involving penetrating arteries of the major arteries, or overt, usually caused by large artery vasculopathy involving the intracranial internal carotid arteries and proximal middle cerebral arteries. Before the age of 20, 11% of SCA patients get a CVA, which is typically ischaemic[11].

Therefore, preventing CVA is a crucial component of providing sickle cell disease children with comprehensive treatment, particularly those between the ages of 2 and 16. Transcranial Doppler (TCD) ultrasonography is used for this on a regular basis in the majority of affluent nations, although it is not as common in underdeveloped nations. According to estimates, a 1g/dl drop in steady state haemoglobin is linked to a 1.5–2.0 relative risk of developing CVA. In sickle cell disease, white blood cells contribute to vaso-occlusive episodes. They produce adhesion molecules that help them stick to the vascular endothelium, which encourages the red blood cells to sickle. The likelihood of sickling and vascular injury increases with the white cell level.

Additionally, it has been demonstrated that lowering intravascular haemolysis with blood transfusions or hydroxyurea medication increases cerebrovascular vasodilatory capacity and lowers cerebral blood flow velocities and the risk of cerebrovascular accidents in children with SCA.

This study aimed to describe the blood flow velocities of the major arteries of the brain in SCA children aged 2-16 years and classify their risk category, and assessing its relationship to the packed cell volume and total white blood cell count. Taking into account that Transcranial Doppler ultrasonography has become routine in the management of children with SCA to prevent CVA and that some children may present with CVA even before their first TCD. The findings of this study are also expected to contribute to the body of knowledge presently available on cerebral blood flow velocities and further our comprehension of this important subject.

## Methodology

Participants in the study included 102 children with SCA, ranging in age from 2 to 16. The participants were gathered from the Federal Teaching Hospital's paediatric sickle cell clinic in Owerri, Imo state, Nigeria. The hospital's Research and Ethics Committee gave its approval. Prior to study enrolment, parents/caregivers and patients provided their informed written consent and assent.

### Criteria for Inclusion

During regular clinic visits, patients between the ages of 2 and 16 were progressively included in the study. Using cellulose acetate electrophoresis at alkaline pH, these include eligible patients who were previously diagnosed with SCA as homozygous haemoglobin S disease. All of the patients were in steady state, which is defined as not having experienced an acute illness (pain crisis, fever, or other acute complications related to SCA) or receiving a transfusion during the previous four weeks.

### Criteria for exclusion

Those having the genotype Haemoglobin SC, children under the age of two and older than sixteen, people getting hydroxyurea, people receiving chronic blood transfusions, people with acute illnesses like fever, central nerve infections, severe head injuries, and people taking anticonvulsants.

### Data Collection

Sociodemographic Information: Basic biodemographic information, including age, sex, and prior medical, neurological, and blood transfusion histories, was gathered using a structured questionnaire.

### Sample Collection

The researcher and two qualified research assistants collected the samples. Following clinical assessment, two millilitres of venous blood were aseptically drawn into an EDTA bottle in order to determine the complete blood count. Using a mythic 60 automated haematology analyser, a full blood count was performed with the help of trained medical laboratory staff affiliated with Federal Teaching Hospital Owerri.

**Non-imaging TCD:** A 2-MHz handheld probe attached to a Doppler box was used to assess the cerebral blood flow velocities of all enrolled patients in accordance with the Stroke Prevention in Sickle Cell Disease protocol. The test, known as the Willis circle, monitored and evaluated the blood flow velocity in arteries. TCD creates audible sounds when it strikes a wave in the middle cerebral artery (MCA) and anterior cerebral artery (ACA) that can be heard and recorded. A non-imaging PMD model 150 manufactured by Spencer Technology in Washington was used for the process. The patient was conscious while lying down on a bed during the surgery. Directly on the patient's temporal region (transtemporal window) was a transducer. In order to direct the ultrasound waves towards the blood arteries being examined, the transducer was positioned differently. Multiple measurements were taken on both sides of each vessel, ranging from 40 to 60 mm. The maximal velocity in the left and right cerebral arteries was recorded using the TAMMV. A velocity of ≥200 cm/sec was considered abnormal (high risk), while values above 170 cm/sec but below 200 cm/sec were considered conditional risks. Normal (standard risk) TAMMV was defined as less than 170 cm/sec. Standard risk was regarded as normal velocity for the purposes of this study, whereas conditional risk and high risk were regarded as abnormal velocity.

**Data Analysis:** After being compiled, the data was input into an Excel spreadsheet. The data was analysed using IBM Statistical Package for Social Sciences (SPSS) version 26.0. Frequency tables and figures were used where appropriate to provide a summary of the variables. The data was found to be normally distributed after undergoing normality testing. The mean and standard deviation were used to summarize quantitative variables that had a normal distribution. Frequencies and percentages were produced for categorical variables. The independent t test was used to compare the means of the two groups. Chi square was used to test for differences in proportions. Statistical significance was defined as a p-value of less than 0.05.

## Results

### TAMMV in the anterior and middle cerebral arteries in the study participants

The time average mean maximum velocities ranged between 38.0 and 248.0 cm/sec. The minimum, maximum, mean velocities and standard deviation in the RACA, LACA, RMCA and LMCA are as shown in table I.The lowest velocity was found in the left anterior cerebral artery and the highest in the right anterior cerebral artery. The highest mean velocity was found in the left middle cerebral artery.

**Table I: TAMMV In the anterior and middle cerebral arteries in the study participants**

| | Minimum Velocities (cm/sec) | Maximum Velocities(cm/sec) | Mean Velocities(cm/sec) | Standard Deviation cm/sec |
|---|---|---|---|---|
| *RACA* | 43.0 | 248.0 | 99.4 | 33.7 |
| *LACA* | 38.0 | 228.0 | 111.1 | 38.6 |
| *RMCA* | 41.0 | 242.0 | 116.4 | 37.1 |
| *LMCA* | 44.0 | 246.0 | 128.5 | 38.0 |

RACA –right anterior cerebral artery, LACA –left anterior cerebral artery, RMCA – right middle cerebral artery, LMCA – left middle cerebral artery, TAMMV- time averaged mean maximum velocity

### Pattern of cerebral blood flow

Majority of the participants had standard risk with prevalence of 82.4%, while prevalence of abnormal blood flow velocity (conditional and high risk) was (17.6%). See figure I

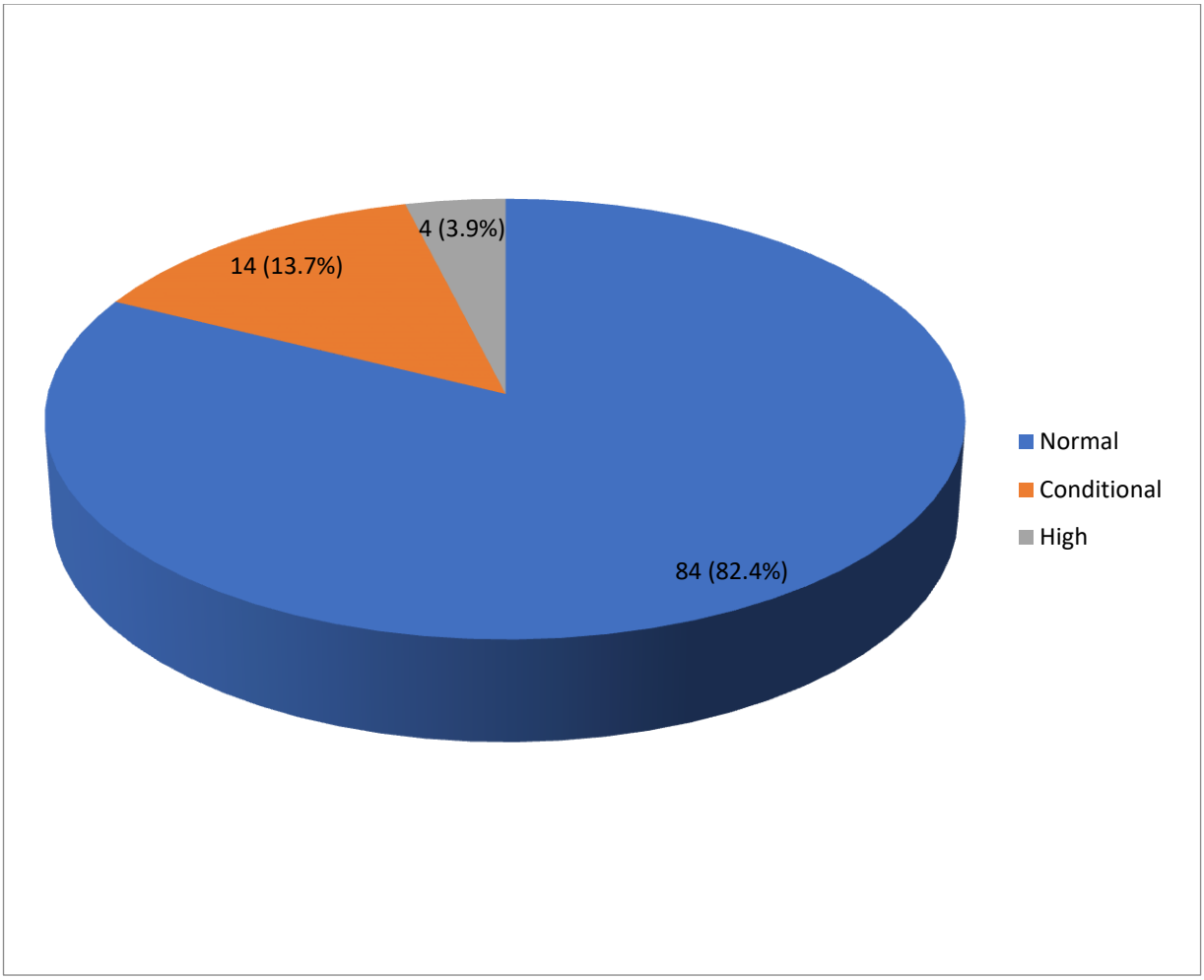


**Figure I: Pattern of the cerebral blood flow velocities**

**Haematological findings of the study participants**

The steady state packed cell volume (PCV) of the study participant ranged from 17% to 33% with mean and standard deviation of 22.74±0.03%. The mean steady state PCV was significantly lower in males than in females (p=0.010). See table II

The range of total white blood cell count for the study participants was 4,600cells/mm$^3$ to 50,000cells/mm$^3$ with mean and standard deviation of 16,233.82± 7,993.92. The mean white blood count was higher in males but the difference was not statistically significant (p=0.337) in average white blood cell between males and females.

**Table II:Haematological findings of the study participants by Gender**

| **Parameter** | **Males** | **Females** **t-test** | **P value** |
|---|---|---|---|
| Steady state PCV(%), mean (±SD) | 22.0 ±0.03 | 24.0 ±0.03 | 0.010* |
| Average WBC count (cells/mm$^3$), mean (±SD) | 16912.3 ±8172.8 | 15374.4 ±7766.8 | 0.337 |

**Relationship between steady state packed cell volume (PCV) and CBFV**

There were no statistically significant correlations between time average velocities in all the arteries and steady state PCV. Coefficient of correlation (R), coefficient of determination ($R^2$) and probabilities are shown in the figure II for the various arteries.

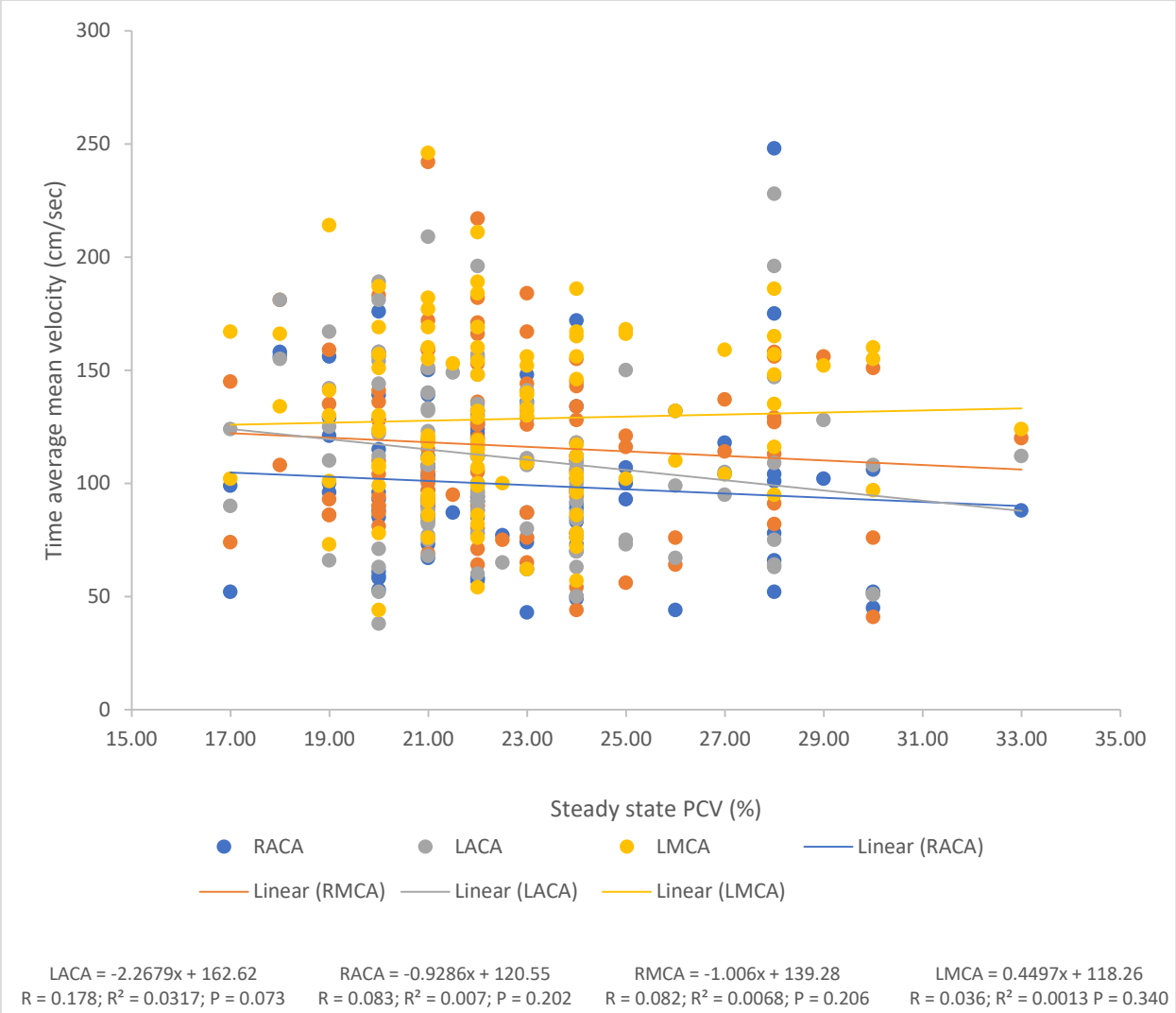


**Figure II: Scattergram showing relationship between steady state PCV and CBFV**

**Relationship between average WBC and CBFV**.

There were no statistically significant correlations between time average velocities in all the arteries and average WBC. Coefficient of correlation (R), coefficient of determination ($R^2$) and probabilities are shown in the figureIII for the various arteries.

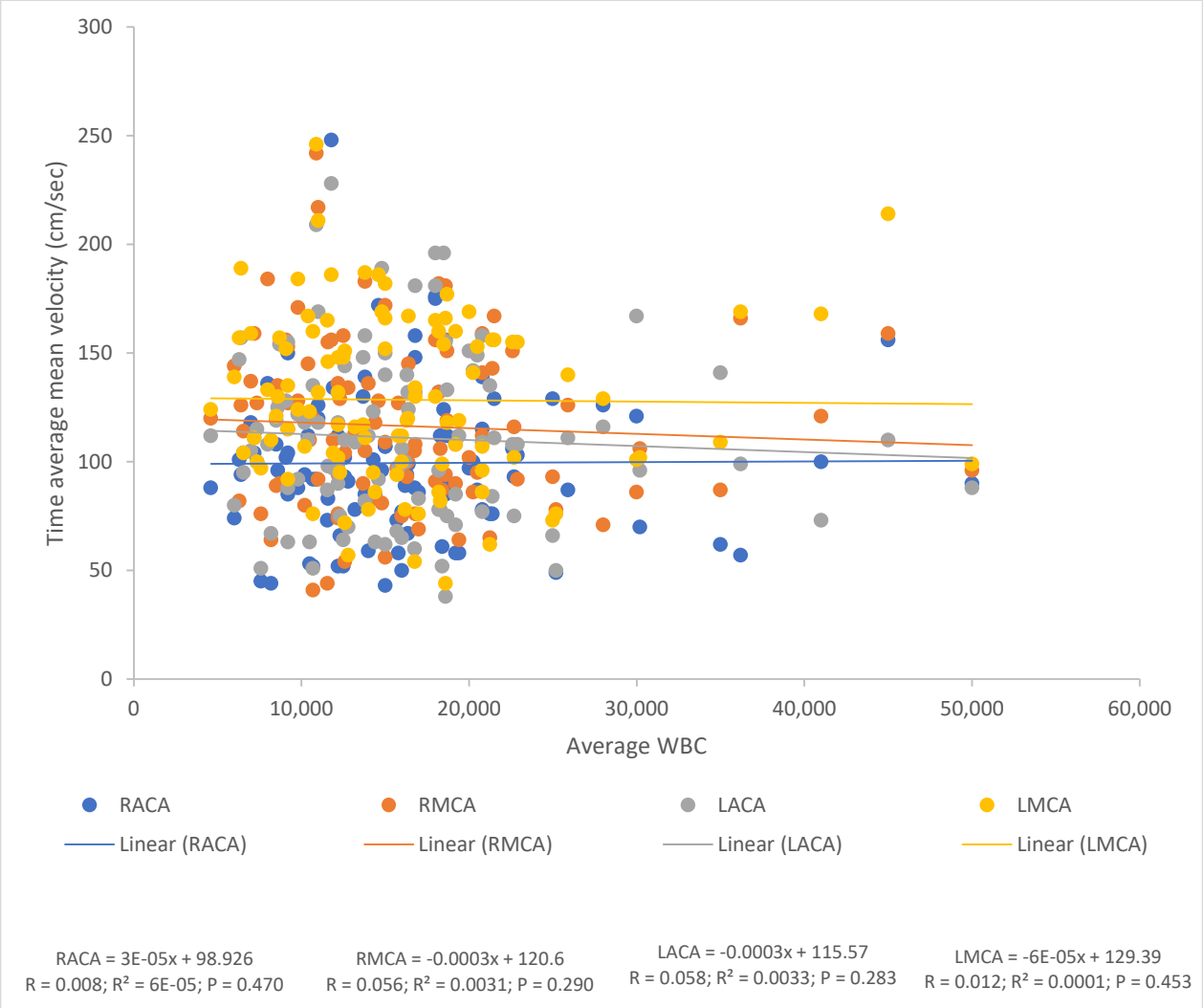


**Figure III: Scattergram showing relationship between average WBC and CBFV**

## Discussion

The TAMMV in this investigation varied between 38.0 and 248.0 cm/sec. The right anterior cerebral artery (RACA) has the fastest velocity, followed by the left middle cerebral artery (LMCA). The left anterior cerebral artery (LACA) has the lowest velocity. This contrasts with the findings of Lagunju et al. [14], who found that the left internal carotid artery (LICA) had the lowest velocity and the left middle cerebral artery (LMCA) had the highest velocity. Additionally, maximal velocity was recorded in the right MCA by Adekunle et al. [13] and Ismail et al. [15]. Ismail et al. recorded minimum velocity in the left terminal internal carotid artery, which is distinct from our study, whereas Adekunle et al. recorded minimum velocity in the left ACA, which is comparable to the current study. Even though the same age group and methods were employed in all the investigations, the authors are unable to provide an immediate explanation for the variations in velocities identified in the various arteries. Even though the majority of research participants had standard risk CBFV, screening and therapies for CVA in SCA must continue because a sizable fraction of the population is still at risk for this potentially fatal complication, for which prevention is always preferable to treatment. This study found that 17.6% of the population had aberrant CBFV, of which 3.9% had high risk for CVA and 13.7% had conditional risk (CR). The majority of children with CR were between the ages of 7 and 11, while all children with high risk CBFV were between the ages of 2 and 6. According to the study's findings, younger children are more likely than older children to have aberrant CBFV. On the other hand, the incidence of high risk CVA in this study is lower than earlier results of 7.8% and 11.5% from a Jamaican and Dallas cohort study, respectively [11]. This is comparable to the prevalence of 4.0% reported from the Cooperative Study of Sickle Cell Disease (CSSCD).

Similar to the 3% reported by Ismail et al. [22] in Kano, the prevalence in Nigeria is lower than the 5.4% reported by Ahmed et al. [17] in Abuja and Fatunde et al. [8] in Ibadan; the 6.3%, 8.4%, and 10.8% reported

by Kehinde et al. [18] in Lagos; Lagunju et al. [14] in Ibadan; and Adekunle et al. [13] in Lagos. The sample sizes used in these research may be the cause of these discrepancies.

In the steady state, the average PCV was 22.74±0.03%. Males had a considerably lower mean steady state PCV than females. The literature has repeatedly shown that low steady state PCV is linked to higher TAMMV and a higher risk of CVA. it has been estimated that 1g/dl decrease in steady state Hb is associated with a relative risk of 1.5 -2.0 for the development of CVA. Lagunju et al [14] showed a negative correlation between haematocrit and Time average maximum mean velocity (TAMMV) as there was a 1.8cm/sec increase in CBF for every 1% decrease in PCV. Additionally, Lagunju et al. [14] in Ibadan and Oniyangi et al. [19] in Abuja discovered that the mean PCV for each participant was 23.6% ± 4.0% and 21.1 ± 3.9%, respectively.

The average number of white blood cells per millimetre was 16,233.82±7,993.92 cells. Males had a higher mean WBC count, although this difference was not statistically significant. White blood cell participate in the vaso-occlusive events seen in sickle cell disease as they express adhesion molecules that promote their adhesion to vascular endothelium thus promoting sickling of the red cells. The higher the white cell count, the higher the chances of sickling and vascular damage.

Even though 10 out of 17 patients with conditioned risks and the four subjects with increased TAMMV had a steady state PCV of less than 23%, the current investigation did not find any statistically significant correlation between low steady state PCV and CBFV. Contrary to this, the authors of the study by Lagunju et al.[14] demonstrated a substantial negative association between low steady state PCV and TAMMV, showing that for every 1% fall in PCV, CBF increases by 1.8 cm/sec. The difference between this study and the one by Lagunju et al.[14] cannot be explained right away.

The mean WBC count in this study was 16,233.82 cells/$mm^3$ ±7,993.92. TWBC and aberrant velocity pattern did not correlate in this investigation. The mean TWBC was 10,448± 4,734 cells/$mm^3$, according to Lagunju et al.,[14] although they pointed out that there was no meaningful relationship between mean WBC and the rise in CBFV.

## Conclusion

Prevalence of abnormal cerebral blood flow velocity is high in Nigerian children with SCA. The packed cell volume was significantly lower in males compared to the female SCA children. There is need to increase the availability of transcranial Doppler ultrasound for routine screening of children with SCA and routine haematological investigations done for all SCA children. This will help in early detection of children at risk of a CVA for prompt intervention that can avert the deadly complication

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**Conflicts of Interest**: Nil

## Authors Contributions

EzeukoLilian : conceptualization, study design, data analysis and interpretation, drafting of the manuscript, reviewing of the manuscript
Odunvbun Magdalene: study design, literature review, data interpretation, revision of the manuscript
Ikejiaku Udochikwuka: study design, literature review, data interpretation, revision of the manuscript
Ike Innocent:study design, literature review, data interpretation, revision of the manuscript
Anthony- Eweputanna Sylvia: study design, literature review, data interpretation, revision of the manuscript
Kawa Alaoma: study design, literature review, data interpretation, revision of the manuscript
Ezerioha Ogechi: study design, literature review, data interpretation, revision of the manuscript
Ezeuko Vitalis: data analysis, data interpretation, revision of the manuscript.

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