

Original article

Association of sickle cell trait in blood donors with baseline hematological and biochemical parameters of whole blood

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Abstract:

Introduction: Sickle cell trait (SCT) exhibits the highest prevalence in Africa. Despite its notable prevalence, SCT is not routinely screened for in African blood services. The presence of SCT in blood donors could potentially impact the baseline quality of whole blood (WB) and may compromise the post-transfusion recovery outcomes for recipients. **Objective:** This study aimed to determine the prevalence of SCT among WB donors and to identify potential associations between SCT status in donors and the baseline hematological and biochemical characteristics of the donated blood. **Materials and Methods:** In this prospective cross-sectional study, WB donors were consecutively enrolled through a systematic sampling approach. Prior to the stripping of the blood bags, a sample from each was analyzed for the presence of hemoglobin-S. Hematological parameters, including blood group, complete blood count, and peripheral blood smear, as well as biochemical parameters, encompassing hemolysis, sodium, potassium, and lactate dehydrogenase levels, were tested on the same day. The association between these parameters and the presence of SCT in donors was evaluated. **Results:** Of 105 donors recruited, 22.86% (n = 24) had SCT and 77.14% (n = 81) did not. Compared to blood donors without SCT, mean corpuscular hemoglobin concentration was significantly lower (34.01 ± 2.30 g/dL vs 34.94 ± 1.44 g/dL, $p = 0.008$) while mean platelet count ($231 \pm 72 \times 10^6/L$ vs $222 \pm 51 \times 10^6/L$, $p = 0.014$) and mean baseline hemolysis ($0.004 \pm 0.03\%$ vs $0.01 \pm 0.08\%$, $p = 0.02$) were significantly higher in blood from donors with SCT. **Conclusion:** SCT significantly influences baseline hematological and biochemical parameters of WB. Therefore, the routine screening of blood donors for hemoglobin-S is recommended as a measure to ensure the safety of transfusions for vulnerable blood recipients.

Keywords : ● Sickle cell trait (SCT) ● Whole blood (WB) ● Baseline hemato-biochemical parameters

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Introduction

Due to optimized resuscitation, logistical simplicity, and reduced donor exposure, whole blood (WB) is increasingly regarded as a viable alternative to multi-component transfusion therapy. As a result, WB is currently being considered for reintroduction into numerous blood transfusion systems globally.¹ This is reassuring to a third of blood services in Sub-Saharan Africa (SSA) who for lack of money, logistics and laboratory equipment cannot produce blood components.² Global safety initiatives typically advocate for the separation of donated blood into components as a more effective utilization strategy. However, a recent study focusing on African children reveals that the administration of WB results in superior hematological recovery and a reduction in the need for re-transfusion compared to the use of packed red blood cells.³ However, the limitations of using WB remain; its shelf life is short and characterized by many time-dependent hematological and biochemical changes that are accounted for by substantial donor-to-donor differences.⁴ Studies from different parts of the world have found the storage performance of blood to vary with sex, body mass index, uric acid levels, frequency of blood donations and dietary habits.⁵⁻⁶ In SSA however, the relationship between donor variability and the quality of WB has been rarely explored. A small-scale study (n = 30) evaluated the hematological and biochemical impact of sickle cell trait (SCT) in citrate-phosphate-dextrose-adenine-1 (CPDA-1) whole blood units. From the seventh day of storage, the authors observed a significant increase in levels of potassium, lactate dehydrogenase (LDH), and hemolysis in WB from SCT donors as compared to that from non-SCT donors.⁷ Based on these findings, they advocate for the routine screening of blood donors for sickle cell hemoglobin (hemoglobin-S) and, in conjunction with other researchers, recommend the deferral of blood donors who are carriers of SCT.⁸

Sickle cell anemia (SCA) is an autosomal recessive hereditary disease caused by a single nucleotide mutation of the β -globin gene that leads to the substitution

of soluble glutamate by insoluble valine at position 6 of the β -globin chain.⁹ The resultant hemoglobin-S polymerizes at low oxygen concentrations into fibrous precipitates. This confers a rigid sickle shape to the red blood cell that can no longer go through the capillary bed, leading to vascular occlusion and ischemia.¹⁰ The SCT is a benign state that occurs in approximately 300 million people worldwide, with the highest prevalence (40%) in SSA. It describes a heterozygous condition in which a person produces both normal hemoglobin AA and abnormal hemoglobin-S, presenting symptoms only when deprived of oxygen or while severely dehydrated.¹¹ In SSA, 19.8 to 26.1% of blood donors carry a SCT.⁷ Despite indications that blood from donors with this trait may deteriorate more rapidly during storage, routine screening for hemoglobin-S is not established in many regions of SSA. The rationale for this omission is often attributed to several factors, including financial constraints, the rapid turnover of blood units, and concerns that excluding donors with SCT would exacerbate the already fragile blood supply, potentially leading to a reduction in available donations.¹² In the pursuit of achieving blood sufficiency, many blood services are reluctant to exclude up to 25% of prospective donors due to concerns about the potential for in vitro quality deterioration that would manifest only days after the blood has been collected and subsequently transfused. Meanwhile, SCT in blood donors may affect the quality of donated blood right at baseline and be unsafe to the blood receiver no matter the duration of storage. The aim of this study was therefore to determine the association of SCT in WB donors with in vitro hemato-biochemical quality of WB at baseline.

Materials and Methods

Study design

The present prospective cross-sectional study was carried out in the Yaoundé University Teaching Hospital (YUTH) over a four-month period from May 1st to August 31st 2023. The study was approved by the institute's

ethics committee (No. 5023/UYI/FMBS/VDRC/DAASR/CSD dated February 6th 2023) and written informed consent was obtained from blood donors. WB units collected either in-house or during mobile blood donation drives were screened according to the national guidelines.¹³ A systematic consecutive sampling approach was employed to select blood donors for the study. Donors who did not meet the eligibility criteria (specifically, those with blood collection exhibiting technical errors or those reactive for any transfusion-transmitted infection) were excluded from participation. Demographic and donor-related characteristics, including age, sex, donation frequency, and blood group, were systematically documented using pre-structured data collection forms.

Blood collection

Whole blood was collected from enrolled blood donors in a single blood bag with 450 mL capacity and 63 mL of CPDA-1 anticoagulant through a single venipuncture. Prior to the removal of the blood bag from its collection set, a sample was obtained in both an ethylene diamine tetra-acetic Acid (EDTA) tube and a plain vial for the purposes of this study. Subsequent to sample collection, the remaining content of the whole blood bag was managed in accordance with the routine standard operating procedures of the YUTH Blood Bank.

Laboratory analysis

Blood collected in the EDTA tube was initially analyzed using an automated cell counter (HumaCount 30 TS, HUMAN Diagnostics Worldwide Co., Ltd., Magdeburg, Germany) to perform a complete blood count. This analysis provided measurements of white blood cells (WBC) count, red blood cells (RBC) count, platelets (PLT) count, mean cell hemoglobin (MCH), mean cell volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). Subsequently, hemoglobin-S screening was conducted utilizing the rapid hemoglobin solubility test (Anamol Laboratories Pvt. Ltd., Palghar, India). Following these procedures, a peripheral blood smear was prepared and stained using the May-Grünwald-Giemsa staining technique.¹⁴

The plain vial was centrifuged at 3,000 x g for five minutes with a tabletop centrifuge (EBA 200S HETTICH Ltd., Tuttlingen, Germany) to yield serum. The serum sample was subjected to an electrolyte (sodium, potassium and chloride) test using an electrolyte analyzer (GE 300 Genrui Biotech Co., Ltd., Shenzhen, China), to LDH test using a semi-automated spectrophotometer (Kenza Max BiochemisTRY, BIOLABO S.A.S Les Hautes Rives, France) and to a serum hemoglobin test using a cell counter (HumaCount 30 TS HUMAN Diagnostics Worldwide Co., Ltd., Magdeburg, Germany). Baseline hemolysis was calculated according to the formula: Hemolysis (%) = [(100-hematocrit) x (serum Hb (g/dL))] ÷ Hb of whole blood (g/dL).

Categorization for analysis

Based on hemoglobin-S screening, blood donors were classified into two groups: those with SCT and those with normal hemoglobin (non-SCT). Proportions of donors with and without SCT were compared across different socio-demographic groups such as gender, age, profession and donor type. To investigate the impact of deferring SCT blood donors on the blood supply, we also compared the proportions of frequent blood donors and the distribution of ABO-Rhesus blood groups between the SCT and non-SCT donor groups. Additionally, we examined the relationship between the presence of SCT and various hematological and biochemical parameters previously measured, as detailed in the laboratory analysis subsection. The hematological quality of the blood was assessed using indicators such as WBC count, PLT count, RBC count, hemoglobin (Hb) concentration, MCV, MCHC, and MCH. Biochemical quality was evaluated through parameters including sodium (Na), potassium (K), chloride (Cl), LDH and the percentage of hemolysis. These specific parameters were selected for analysis to provide a comprehensive evaluation of both hematological and biochemical blood quality.

Statistical analysis

According to Carillo-Esper et al.¹⁵, the proportion of whole blood units with bio-mechanical abnormalities at

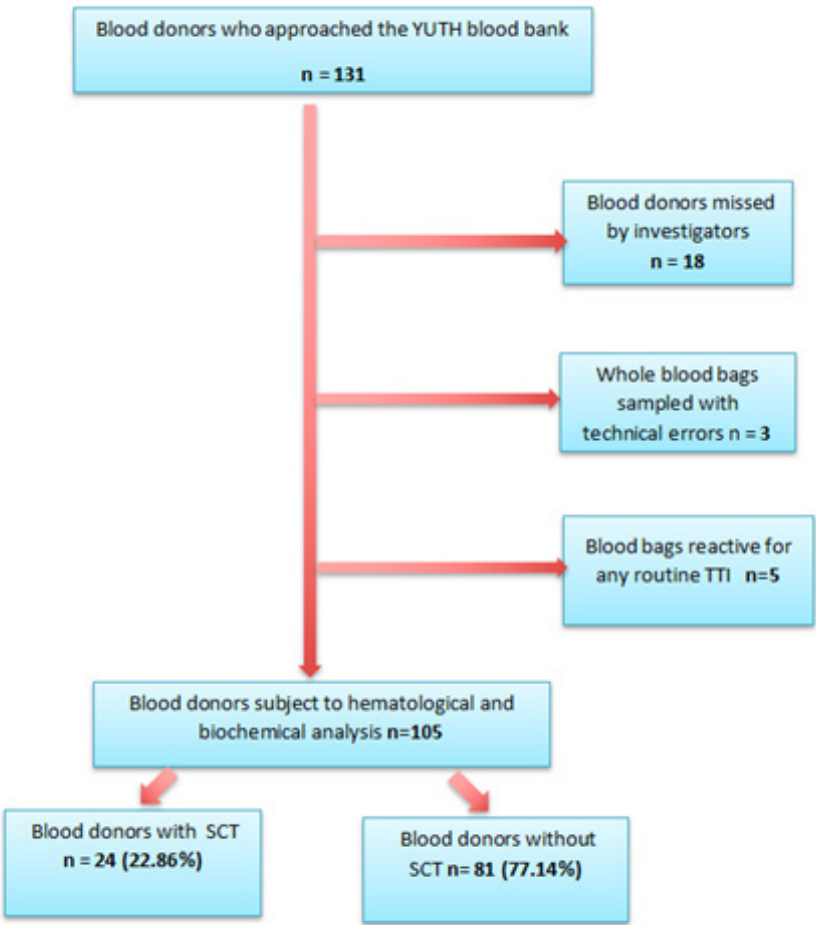
baseline is 40.2%. The sample size was calculated to be 93 subjects at a confidence level of 95% and absolute precision of 0.1. Considering that up to 12.5% of WB units are discarded in certain parts of Cameroon for reacting to one or more of the four routinely screened transfusion transmitted infections (TTIs) including human immunodeficiency virus, syphilis, hepatitis B virus and hepatitis C virus,¹² 12 more subjects were included.

Data analysis was conducted using IBM SPSS Statistics version 23. The data were assessed for normal distribution, which was confirmed across all variables. Qualitative variables were described in terms of proportions and analyzed using the Pearson chi-square test to examine differences between groups. Quantitative variables were compared against reference ranges established by the African Society of Blood Transfusion¹⁶ and were summarized using mean values and standard

deviations. To assess differences in mean values of hematological and biochemical variables between the SCT and non-SCT populations, a student's t-test was employed. The threshold for statistical significance was established at a p-value of 0.05.

Donor characteristics

Of the 131 blood donors who presented at the YUTH Blood Bank, 18 of them were missed by the research investigators. Additionally, three blood units were excluded from analysis due to technical errors during sampling, which resulted in visible hemolysis or coagulation in the blood bags. Furthermore, five units were discarded due to reactivity to TTIs. Consequently, data from 105 blood donors were utilized for the study. A detailed flowchart of the study population selection process is illustrated in Figure 1.



YUTH = Yaoundé University Teaching Hospital; TTI = transfusion transmitted infection; SCT = sickle cell trait

Figure 1 Flow chart showing retention of blood donors for this study

Results

In this study, 22.86% (n = 24) of donors had SCT and 77.14% (n = 81) had no SCT. Since sickle cell trait was screened by a qualitative rapid solubility test, the quantity of hemoglobin-S was not measured. The mean age of the study population was 29.9±8.1 with a range of 19-58 years. The majority of blood donors were male (n = 74, 70.5%), voluntary non-remunerated (n = 84, 80%) and rhesus positive (n = 99, 94.3%).

Association of blood donor characteristics with SCT

The prevalence of SCT in blood donors was statistically similar between different age, sex, profession and donor type groups. There were as many first time donors (n = 53) as frequent donors (n = 52). Sixteen (30.7%) frequent donors had a donation frequency of thrice yearly. There was no significant difference in the proportion of rare blood groups [Odds ratio (OR):

0.49, 95% confidence interval (CI): 0.38 to 6.36, *p*-value: 0.56, Table 1] nor of frequent blood donations (OR: 0.74, 95%CI: 0.28 to 1.95, *p*-value: 0.54, Table 1) between blood donors with SCT and those without SCT.

Association of baseline hematological parameters with SCT

Mean values of hematological parameters of WB from both donors with SCT and those without SCT lay within reference ranges. Significantly lower mean MCHC (*p*-value: 0.008, Table 2) and higher mean platelet count (*p*-value: 0.014, Table 2) values were observed in whole blood from donors with SCT than donors without SCT.

Abnormally shaped red blood cells (aRBCs) were found in peripheral blood smears of 47 (58%) donors without SCT and in 17 (70.8%) of those with SCT but the difference in proportion was not statistically significant (OR: 0.59, 95%CI: 0.21 to 1.60, *p*-value: 0.33).

Table 1 Comparison of the prevalence of sickle cell trait within different socio-demographic groups of blood donors

Donor characteristics		Hemoglobin genotype			
Frequency (n, %)		Non -SCT 81 (77.1)	SCT 24 (22.9)	OR (95%CI)	<i>p</i> -value
Age (years)	< 35 (79, 75.2)	61 (58.1)	18 (17.1)	1.02 (0.36-2.91)	0.55
	> 35 (26, 24.8)	20 (19)	6 (5.8)		
Gender	Male (74, 70.5)	60 (57.1)	14 (13.3)	2.04 (0.79-5.23)	0.20
	Female (31, 29.5)	21 (20)	10 (9.5)		
Profession	Student (49, 46.7)	40 (38.1)	9 (8.6)	1.63 (0.64-4.14)	0.31
	Worker (56, 53.3)	41 (39.0)	15 (14.3)		
Donor type	VD (84, 80)	66 (62.9)	18 (17.1)	1.47 (0.50-4.32)	0.49
	RD (21, 20)	15 (14.3)	6 (5.7)		
Donor frequency	FTD (53, 50.5)	42 (40)	11 (10.5)	1.23 (0.51-3.17)	0.60
	FD (52, 49.5)	39 (37.1)	13 (12.4)		
ABO-Rhesus blood group	O Rh + (58, 55)	11 (10.5)	47 (44.7)	0.74 (0.28-1.95)	0.54
	A Rh + (23, 21)	6 (5.7)	17 (16.2)		
	B Rh + (13, 12.4)	2 (1.9)	11 (10.5)		
	AB Rh + (5, 4.8)	3 (2.9)	2 (1.9)		
	O Rh - (3, 2.9)	1 (0.9)	2 (1.9)		
	B Rh - (3, 2.9)	1 (0.9)	2 (1.9)		

Note: Comparisons made by Pearson's Chi square test and Fisher's exact test when more than 20% of cells have a less than 5 count. Hemoglobin genotype assessed by rapid hemoglobin solubility test.

SCT = sickle cell trait; OR = odds ratio; CI = confidence interval; VD = voluntary donor; RD = replacement donor; FTD = first time donor; FD = frequent donor; Rh = rhesus; + = positive; - = negative

Table 2 Comparison of mean hematological parameters of whole blood units from SCT blood donors and non-SCT blood donors

Hematological variable	Hemoglobin genotype	Reference range	Mean	SD	p-value	95% confidence interval	
						Lower	Upper
WBC	Non SCT	4.5-11.0x10 ⁹ /L	4.57	1.26	0.871	-.37	.78
	SCT		4.37	1.21		-.37	.78
RBC	Non SCT	3.5-5.5x10 ¹² /L	4.65	0.72	0.341	-.40	.31
	SCT		4.69	0.93		-.46	.37
Hemoglobin	Non SCT	11.5-17.5 g/dL	13.54	1.94	0.106	-.74	1.19
	SCT		13.32	2.57		-.93	1.38
MCV	Non SCT	80-100 fl	83.34	6.79	0.130	-3.14	3.98
	SCT		82.92	10.32		-4.15	5.01
MCH	Non SCT	26-34 pg	29.19	2.74	0.059	-.64	2.23
	SCT		28.39	4.14		-1.04	2.64
MCHC	Non SCT	32-36 g/dL	34.94	1.44	0.008	.17	1.71
	SCT		34.01	2.30		-.08	1.95
Platelet count	Non SCT	150-400x10 ⁹ /L	222.18	51.12	0.014	-35.32	16.78
	SCT		231.45	72.20		-41.52	22.98
aRBCs	Non SCT	< 2,000/mm ³	976.72	5,007.05	0.749	-2,519.99	1,673.95
	SCT		1,399.75	2,343.04		-1,882.13	1,036.09

Note: Bold *p*-values indicate statistically significant results. n = 24 for SCT (sickle cell trait) n = 81 for non-SCT (normal hemoglobin) SD = standard deviation; WBC = white blood cells count; RBC = red blood cells count; MCV = mean cell volume; MCH = mean cell hemoglobin; MCHC = mean corpuscular hemoglobin content; aRBCs = abnormally shaped red blood cells.

p-value calculated with student t-test.

These aRBCs included echinocytes (crenated cells with several spurs), drepanocytes (elongated or S-shaped cells pointed on each end), schistocytes (fragmented cells with a bitten appearance), codocytes (bull eye looking cells), dacrocytes (cells shaped like a tear or pear), eliptocytes (cigar-shaped cells) and ovalocytes (egg-shaped cells), as shown in Figure 2. The mean number of aRBCs in peripheral blood smears from donors with SCT was comparable to that of those from donors without SCT (*p*-value: 0.749, Table 2).

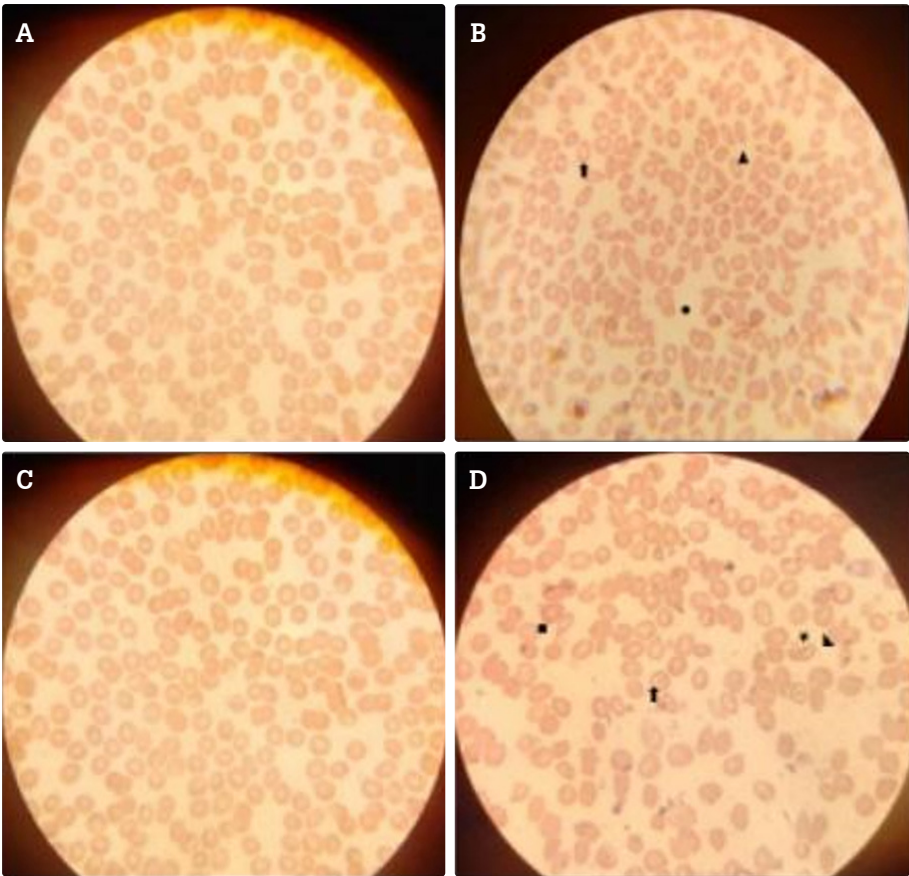
Association of baseline biochemical parameters with SCT

All mean values of biochemical parameters from donors with SCT and from those without SCT were observed to be within reference ranges. Baseline hemolysis did not exceed the permissible limit of 0.8% in WB from

both SCT and non SCT donors but the mean value was significantly higher in donors with SCT than in donors without SCT (*p*-value: 0.02, Table 3).

Discussion

WB constitutes the fundamental substrate for component production and remains one of the most frequently utilized blood products across many regions of SSA. The question of whether individuals with SCT should be deferred from blood donation has emerged as a pertinent issue in recent years. However, the existing evidence base addressing this question is notably limited in low-income countries such as ours. In this study, we sought to elucidate the associations between baseline hematological and biochemical parameters and the



A: normal biconcave disc cells in blood from a donor without sickle cell trait. B: Abnormally shaped red blood cells in the blood of a donor without sickle cell trait showing echinocyte (circle), eliptocyte (triangle) and ovalocyte (arrow). C: normal biconcave disc cells in blood from a donor with sickle cell trait. D: abnormally shaped red blood cells in the blood of a donor with sickle cell trait showing drepanocytes (star), dacryocytes (rectangle), codocyte (arrow) and schistocyte (triangle).

Figure 2 Sample images of May-Grünwald-Giemsa stained peripheral blood smears (100x) of whole blood units at baseline.

Table 3 Comparison between mean biochemical parameters of whole blood units from SCT and non-SCT blood donors

Biochemical variable	Hemoglobin phenotype	Reference range	Mean	SD	p-value	95% confidence interval	
						Lower	Upper
% hemolysis	Non SCT	< 0.8%	0.004	0.03	0.02	-0.04	0.01
	SCT		0.00	0.08		-0.05	0.022
Na	Non SCT	137-151	140.07	4.84	0.97	-3.36	1.22
	SCT		141.13	5.37		-3.55	1.41
K	Non SCT	3.4-5.8	3.79	0.62	0.61	-0.42	0.16
	SCT		3.9	0.694		-0.41	0.19
Cl	Non SCT	98-109	105.38	6.62	0.83	-6.33	-0.19
	SCT		108.6	6.82		-6.45	-0.08
LDH	Non SCT	225-450	430.70	122.31	0.38	-61.71	51.19
	SCT		435.96	123.00		-63.08	52.56

Note: Bold *p*-values indicate statistically significant results. n = 24 for SCT (sickle cell trait) n = 81 for non-SCT (normal hemoglobin) SD = standard deviation; % = percentage; Na = sodium; K = potassium; Cl = chloride; LDH = lactate dehydrogenase. *p*-value calculated with student t-test.

presence of SCT in WB donors through in vitro analyses. Our findings reveal that, in addition to a lower MCHC, elevated platelet counts, and increased baseline hemolysis, the mean hematological and biochemical values of WB from donors with SCT were generally comparable to those from donors without SCT.

Blood donors with SCT exhibited comparable socio-demographics, donation frequencies and similar distributions of ABO-Rh blood groups relative to non-SCT donors. Consequently, excluding SCT donors would further diminish an already strained blood supply, given that the proportion of SCT donors would directly impact the overall availability of blood products. In SSA, where the global prevalence of SCT is the highest, the adoption of such a policy should not be pursued without substantial evidence demonstrating potential harm associated with the transfusion of whole blood from SCT-positive donors.

Our analysis revealed a fascinating trend: the average MCHC value in WB from SCT donors was lower compared to non-SCT donors. As a reminder, MCHC is a measure obtained by dividing hemoglobin by hematocrit.¹⁷ While the hemoglobin difference between the two groups wasn't statistically significant, it was consistently lower in SCT blood, potentially explaining the observed decrease in MCHC.

Interestingly, this finding contrasts with the typical presentation in SCA patients who often have higher than normal MCHC due to smaller cell volume, which is thought to worsen the rheological properties (flow characteristics) of their sickle cells.¹⁸ In fact, some research suggests that lowering MCHC might have an anti-sickling effect in SCA patients.¹⁹

This raises a curious question: could transfusing blood from SCT donors to SCA patients be beneficial due to the potential MCHC reduction? While ethical considerations are paramount,²⁰ this warrants further investigation to explore this possibility.

Peripheral blood smear evaluations revealed a non-significant elevation in aRBC counts among SCT donors compared to their non-SCT counterparts. These findings align with observations reported by Wilson, et al.²¹ where 96% of peripheral blood smears from SCT donors contained aRBCs, compared to only 4% in non-SCT individuals. The potential implications of these aRBCs persisting beyond the shelf life of whole blood units and negatively impacting post-transfusion recovery in recipients warrant further investigation. Notably, a comprehensive analysis exploring the precise relationship between aRBC prevalence in whole blood from SCT donors and the recovery outcomes of blood recipients remains absent in current literature. Meanwhile, certain researchers have observed aRBCs in donors with high body mass index⁶. More so, there may be other unscreened traits of hemoglobinopathies (like thalassemia) and membranopathies (hereditary spherocytosis) among non-SCT blood donors that could contribute to the expression of aRBCs.

It was observed in this study that mean platelet count was higher in blood donors with SCT than in those without SCT. While most studies find comparable numbers of platelets among SCT and non-SCT populations²², one study in Ghana similarly observed mean platelets at baseline to be higher in blood donors with SCT than in those without SCT.⁷ This suggests higher thrombopoiesis in persons with SCT. Also, SCT provides a survival advantage against malaria fatality over people with normal hemoglobin in regions where malaria is endemic²³ and malaria infections almost always lower platelet count.²⁴ The lower incidence of malaria infection in donors with SCT compared to donors without SCT could justify the higher mean platelet count value observed in SCT blood donors.

This study observed a higher mean baseline hemolysis rate in blood donors with SCT compared to non-SCT donors. The elevated number of aRBCs identified in peripheral blood smears of SCT donors may provide a potential explanation for this finding. Previous research

suggests that the altered cell membrane and reduced deformability characteristic of aRBCs contribute to increased biomechanical fragility, rendering them more susceptible to hemolysis.²⁵

While Aninaghei et al. reported no initial hemolysis in either SCT or non-SCT whole blood units,⁷ his study demonstrates hemolysis in SCT blood exceeding the acceptable limit of 0.8% after seven days of storage, and progressively increasing with each subsequent week compared to non-SCT blood. It is important to note that most whole blood transfusions in Sub-Saharan Africa (SSA) occur within seven days of storage.¹² In our study, we found blood from SCT donors at baseline to have higher hemolysis than blood from non-SCT donors but the permissible limit of 0.8% was not exceeded. This low and acceptable level of hemolysis observed may explain why other indicators of red blood cell splitting such as K, Na and LDH still lay within normal limits. Nevertheless, the findings presented here underscore the importance of implementing routine hemoglobin-S screening of blood donors. This practice aligns with existing CDC guidelines that prohibit the use of SCT blood for neonatal transfusions, transfusions in patients with SCA, and massive transfusions.²⁰ For the continued safety of general blood recipients, further research may be warranted to explore the potential benefits of shortening the shelf life of WB derived from SCT donors, particularly to a timeframe before hemolysis reaches unacceptable levels.

This study had a few limitations. Due to time and financial constraints, hemoglobin-S screening (not hemoglobin electrophoresis) was used to segregate donors as SCT and non-SCT. The association of SCT and recipient outcomes was not measured. Due to the cross-sectional nature of our study design, there was unequal distribution of SCT and non-SCT donors. As such, causal relationships with hematological and biochemical parameters of blood units could not be confidently established.

Conclusion

Sickle cell trait does influence baseline hematological and biochemical parameters of whole blood. To gain a more comprehensive understanding of how sickle cell trait affects the acceptability and storage efficiency of whole blood, future research should adopt cohort studies with larger sample sizes.

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