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High birth prevalence of sickle cell disease in Northwestern Tanzania

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Abstract

Background—Worldwide, hemoglobinopathies affect millions of children. Identification of hemoglobin disorders in most sub-Saharan African countries is delayed until clinical signs of the disease are present. Limited studies have been conducted to understand their prevalence and clinical presentation among newborns in resource-limited settings.

Methodology—This was a prospective cohort study. Newborns (aged 0–7 days) at two hospitals in Northwestern Tanzania were enrolled and followed prospectively for 6 months. Clinical and laboratory information were collected at baseline. Participants were screened for hemoglobinopathies using high-performance liquid chromatography. Clinical and laboratory follow-up was performed at 3 and 6 months for those with hemoglobinopathies as well as a comparison group of participants without hemoglobinopathies.

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*These authors contributed equally to the supervision of this study.

Authors Contribution

E.A., L.S., A.M., N.K., E.K., and J.M. conceived the idea, designed the experiments, and coordinated the study; E.A., T.M., N.C., and R.K. participated in sample collection; E.A., L.S., A.M., and J.M. performed the experiments; E.A., A.M., N.K., J.M., and R.P. analyzed data and interpreted the results; E.A., L.S., A.M., N.K., E.K., and J.M. contributed reagents, materials, and analysis tools; E.A., L.S., A.M., N.K., E.K., R.P., and J.M. wrote the manuscript. All authors read, edited, and approved the final version of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Results—A total of 919 newborns were enrolled. Among these, 1.4% (13/919) had sickle cell anemia or Hb S/ β^0 -thalassemia (Hb FS), and 19.7% (181/919) had sickle cell trait or Hb S/ β^+ -thalassemia (Hb FAS). Furthermore, 0.2% (two of 919) had β^+ -thalassemia. Red cell indices compared between Hb FS, Hb FAS, and Hb FA were similar at baseline, but hemoglobin was lower and red cell distribution width was higher in children with Hb FS at 3- and 6-month follow-up. Febrile episodes were more common for children with Hb FS at 3- and 6-month follow-up.

Conclusion—The prevalence of sickle cell disease among neonates born in Northwestern Tanzania is one of the highest in the world. Newborn screening is needed early in life to identify neonates with hemoglobinopathies so that clinical management may commence and morbidity and mortality related to hemoglobinopathies be reduced.

Keywords

newborn; Northwestern Tanzania; sickle cell anemia; sickle cell disease; sickle cell trait; thalassemia

1 Introduction

Hemoglobinopathies, such as sickle cell disease (SCD), and thalassemia are genetically inherited, widely distributed, and affect millions of people around the world.¹ Of the estimated 330,000 neonates who are born worldwide annually with a major hemoglobinopathies, 275,000 have SCD, and the overwhelming majority of these are born in sub-Saharan Africa (SSA).² Mortality related to SCD and thalassemia is highest in the first 3 years of life.^{3,4} In rural parts of SSA, most children with SCD die before the age of 5. In urban centers in SSA, great gains have been made, but early childhood mortality is still 10 times higher than the United States.^{6–8} Hemoglobinopathies are responsible for 6.4% of all mortality among children under 5 years of age in SSA.²

To address this high mortality rate, the World Health Organization has recommended that countries with a high prevalence of SCD implement a national strategy for diagnosis and treatment, including the creation of a newborn screening program.⁹ High-income countries have drastically decreased mortality over the past few decades with the introduction of early infant diagnosis and comprehensive care programs.¹⁰ Because of economic constraints, newborn screening of hemoglobin disorders in most SSA countries has been limited, and diagnosis is often delayed until children present with clinical signs of disease.

Tanzania has the third highest number of SCD-related births in the world annually. Tanzania does not have a national newborn screening policy, but it has taken great strides in the diagnosis and management of SCD, recognizing its public health importance and creating national guidelines for care of people affected by SCD.^{11–13} Most of the research and clinical care has been focused in the coastal city of Dar es Salaam at the national hospital.^{7,14} We have previously reported the high morbidity from SCD in the Northwestern part of the country where the sickle cell gene is thought to be most prevalent.^{15,16} However, estimates of SCD prevalence are based primarily on small adult populations conducted half a century ago,^{17,18} and recent reports have shown that SCD prevalence based on Hardy–Weinberg equilibrium from such studies are unreliable.¹⁹

Therefore, we conducted a study to understand the extent of hemoglobinopathies, specifically to generate baseline information on its prevalence and clinical pattern among newborns in two selected hospitals in Northwestern Tanzania. Our secondary objective was to understand the changes in hematological parameters in those affected by hemoglobinopathies compared to unaffected newborns. These data will provide a foundation for planning a coordinated public health response that targets interventions at the populations most affected by SCD. This will result in reduction of morbidity and improved survival of the affected children.

2 Methods

2.1 Study area and recruitment

This prospective cohort study was conducted among newborns in the Department of Paediatrics and Child Health of Bugando Medical Centre and Sekou Toure Hospital in Northwestern Tanzania. Bugando Medical Centre (BMC) is a zonal referral hospital as well as a consultant and tertiary specialist teaching hospital responsible for care of all the Lake and Western Zones of the United Republic of Tanzania. Sekou Toure Hospital (STH) serves as the Regional Referral Hospital for Mwanza region. The catchment area of these centers includes nine regions with a population of approximately 16.2 million people (Fig. 1). The two hospitals have approximately 2,300 births per month. BMC has a sickle cell clinic which has >400 children enrolled. The clinic runs once a week, and about 30 patients are seen on a weekly basis. Most of the children report to the clinic after development of complications such as dactylitis, recurrent fever, or vaso-occlusive crisis. Children with SCD at BMC are provided an insecticide-treated bed net (ITN) and prescribed daily folic acid and penicillin. Formerly, chloroquine was prescribed for malaria prophylaxis, but this was stopped due to widespread resistance of malaria to chloroquine. Due to the cost and availability of other antimalarial medication, ITNs are the primary method of malaria prophylaxis currently employed.

The initial study enrolment was conducted from August 2014 to September 2014. Newborns aged 7 days old with no history of blood transfusion at enrolment were recruited consecutively from the neonatal wards of the respective hospitals. After written informed consent was obtained from the parents or guardians of neonates, demographic and clinical information was collected using a standardized questionnaire. A venous blood sample was then collected for examination of a complete blood count (CBC) and screening for hemoglobinopathies (see Section 2.2).

All babies with sickle cell anemia or Hb S/ β^0 -thalassemia (Hb FS) were selected for a follow-up phase. In addition, two comparison groups were created for follow-up: a randomly selected group of approximately 100 neonates with normal hemoglobin (Hb FA) and a randomly selected group of approximately 100 neonates with sickle trait (Hb FAS). Follow-up was conducted at 3 months and 6 months of age. At each follow-up, vital status, history of febrile illness, history of hospital visits due to illness, and a record of immunizations were obtained. Venous blood samples were collected and evaluated to determine fetal hemoglobin (Hb F) percent at 3 months and other hematological parameters at 3 and 6 months.

2.2 Laboratory methods

Peripheral venous blood was collected in ethylenediaminetetraacetic acid tubes at enrolment from all neonates and at 3 and 6 month follow-up visits from infants enrolled in the follow-up phase. A CBC was performed using the Cell-Dyn 3700 Hematology Analyzer (Abbott Diagnostics, Lake Bluff, IL) at STH. Samples were shipped to the Muhimbili University of Health and Allied Sciences sickle cell laboratory for hemoglobinopathy screening using high-performance liquid chromatography (HPLC). HPLC was performed using the Variant I Haemoglobin Testing System (Bio-Rad Laboratories, Inc., Hercules, CA) under the experimental conditions specified by the manufacturer. The principle, reagents, sample collection and preparation, and interpretation of reports of HPLC have already been explained elsewhere.^{20,21} β^+ -Thalassemia was diagnosed when the peak in the A₂ window was >4.0%.

2.3 Data analysis

Data were analyzed using STATA version 12 (Stata Corp, College Station, TX). Differences in proportion were analyzed using a chi-squared or Fishers exact test where appropriate. For comparison of mean hematological parameters between groups, a Wilcoxon rank sum test or Kruskal-Wallis test was used where appropriate. A *P*-value < 0.05 was considered statistically significant.

2.4 Ethical issues

Ethical clearance for this study was obtained from the combined Catholic University of Health and Allied Sciences and BMC research ethics committee with research certificate number BREC/001/36/2014. Ethical approval was also obtained from the Institutional Review Board of Weill Cornell Medicine. Written informed consent was obtained from the parent or guardian of each neonate. All neonates with severe hemoglobinopathies were invited to return to clinic for discussion of abnormal test results by 8 weeks of life. Those with SCD were counselled, initiated on penicillin and folate prophylaxis, and registered to attend our sickle cell clinic at BMC.

3 Results

3.1 Enrolment and follow-up

A total of 2,280 deliveries occurred during the period of enrolment: 1,300 at BMC and 980 at STH. The parents of 919 neonates were approached and screened for enrolment during the days and times that the research assistants were available at the clinical sites. None of the parents declined participation, and all 919 neonates were enrolled. Out of these, 430 (46.8%) neonates were from BMC, 477 (51.9%) were from STH, and 12 (1.3%) were delivered in other nearby hospitals and admitted to the neonatal wards of BMC or STH before 1 week of age due to need for observation (Fig. 2). A total of 216 neonates were selected for follow-up: 13 neonates with Hb FS, 96 neonates randomly selected with Hb FAS, and 107 neonates randomly selected with Hb FA.

At 3 months, the parents of 156 neonates (72.2%) who were selected for follow-up were reached by phone and their febrile history, immunizations, admissions, and death history

were obtained, while 127 neonates (58.8%) attended the follow-up clinic for hematological testing. At 6 months, the parents of 135 infants (62.5%) were reached by phone and their febrile history, immunization, admissions, and death history were obtained, while 102 neonates (47.2%) attended the follow-up clinic for laboratory testing. Families who could not be reached by mobile phone to provide a clinical history for their child were considered completely loss to follow-up (LTFU). Follow-up laboratory data were unavailable for some patients who were reached by phone but were unable to return to the study site for laboratory testing. Details concerning enrolment and LTFU at 3 and 6 months are shown in Figure 2.

3.2 Prevalence of hemoglobinopathies

The distribution of hemoglobin variants identified among the study participants is shown in Figure 3. Abnormal hemoglobins were detected in 197 of 919 (21.4%) neonates. Of the 919 screened neonates, 181 of 919 (19.7%) had sickle cell trait (SCT) or compound sickle cell/ β^+ -thalassemia (Hb FAS), 13 of 919 (1.4%) had SCD or compound sickle cell/ β^0 -thalassemia (Hb FS), one (0.1%) neonate had Hb FAD variant, and two (0.2%) had β^+ -thalassemia.

3.3 Clinical characteristics at baseline and follow-up

The median age was 2 days (interquartile range, 1–2 days) (Table 1). There were 486 (52.9%) male neonates enrolled, and 24 (8.9%) were born prematurely (<37 weeks gestational age). HIV exposure was identified in 58 (6.3%), and 131 (14.3%) did not know their HIV exposure history. Very few parents (12, 1.3%) knew whether they had SCT. A sibling with recurrent transfusion was reported in 18 (2.0%) of all patients, but it was more commonly reported by families of children later diagnosed with SCD (six of 13, 46.2%) compared to those with Hb FA (0.8%) or Hb FAS (3.3%) ($P < 0.001$). A similar trend was identified for recurrent jaundice. It was more commonly reported by families of children later diagnosed with SCD (five of 13, 38.5%) compared to those with Hb FA (0.9%) and Hb FAS (2.2%) ($P < 0.001$). These were the only historical features that differed between the groups.

The clinical presentation among the different hemoglobin variants did not differ between different types of hemoglobin except that individuals with Hb FS were more likely to be ill at enrolment (7.7%) compared to individuals with Hb FA (2.1%) and Hb FAS (3.3%) ($P < 0.02$). At 3- and 6-month follow-up, the prevalence of febrile episodes was significantly higher in the Hb FS group (Supplementary Table S1). None of the other parameters differed between the groups.

3.4 Hematological parameters at baseline and follow-up

The percent of fetal hemoglobin was measured in blood samples at baseline and at 3-month follow-up. The baseline mean percent of fetal hemoglobin was significantly higher in the Hb FS group (84.7%) compared to the Hb FA (76.3%) and Hb FAS (77.6%) groups ($P < 0.001$). At 3-month follow-up, the percent of fetal hemoglobin remained higher in the Hb FS group (61.2%) than the Hb FA (34.9%) and Hb FAS (31%) groups ($P < 0.001$) (Table 2).

A CBC was performed at baseline, 3-month, and 6-month follow-up to compare the hematological indices at these time points. The baseline values and the erythrocyte indices that were significantly different at 3 and 6 months are provided in Table 2. At baseline, the Hb FA, Hb FAS, and Hb FS groups had no significant difference in their erythrocyte indices other than the mean corpuscular volume, which was slightly smaller in the Hb FAS group ($P = 0.04$), and the red cell distribution width (RDW), which was slightly smaller in the FA group ($P < 0.001$). Leucocytes were significantly lower in the Hb FS group compared to Hb FA and Hb FAS ($P = 0.019$).

At 3-month follow-up, the RDW remained significantly different, being highest among those with Hb FS (20.87 ± 3.71) compared to those with Hb FA (16.49 ± 3.06) or FAS (15.78 ± 0.36) ($P = 0.002$). At 6-month follow-up, the RDW was no longer different between groups ($P = 0.11$), although the Hb FS group continued to have the widest RDW (18.34 ± 4.04). This was significantly higher than the RDW of the Hb FA group (15.25 ± 5.70) when the two were compared individually ($P = 0.003$). In addition, the red cell number and hematocrit were now significantly different between the three groups. Both were lowest in the Hb FS group.

At baseline, neonates in the different groups had a similar mean hemoglobin ranging from 16.7 g/dl (Hb FA) to 17.7 g/dl (Hb FS) ($P = 0.58$). At 3-month follow-up, a decline in the mean hemoglobin was observed in each group, but the difference between the mean hemoglobins in each group remained similar ($P = 0.11$). The decline in hemoglobin was more pronounced among neonates with SCD (from 17.7 to 8.6 g/dl) compared to both normal neonates (from 16.7 to 10.2 g/dl) and neonates with SCT (16.8 to 10.0 g/dl). At 6 months, mean hemoglobin was significantly different between each of the groups ($P = 0.016$). A further decline in mean hemoglobin was observed in those with SCD and SCT, 7.9 g/dl in those with SCD compared to 9.6 g/dl in those with SCT. There was a slight increase in mean hemoglobin to 10.4 g/dl in normal infants (Fig. 4).

4 Discussion

The birth prevalence of hemoglobinopathies in Northwestern Tanzania is extremely high with 1.4% of children born with Hb FS and one-third of children carrying a significant hemoglobin variant. This is three times higher than the rates reported at the national hospital in the coastal city of Dar es Salaam²² as well as the most recent report among newborns in Northwestern Tanzania,²³ both of which reported Hb FS in only 0.5% of births. We confirm high extrapolated estimates based on older adult populations from around Lake Victoria.^{17,18} The North-western part of the country continues to experience selective pressure for the Hb S allele as it has continuous transmission of malaria throughout the year and the highest prevalence of malaria among children in the country.²⁴ The high prevalence of SCD likely contributes to a significant proportion of under-five mortality in the region, which is the highest in the country.²⁵

The prevalence we identified is significantly higher than the prevalence in middle- or high-income countries in Latin America, Europe, or the United States.^{26–28} Rather, the prevalence in Northwestern Tanzania is consistent with the highest prevalence areas in SSA

such as Nigeria in West Africa (1.6%) or Angola (1.5%) and the Democratic Republic of Congo (1.4%) in Central Africa.^{29–31} A higher prevalence of SCD among newborns has rarely been reported. A smaller cross-sectional study at Mulago Hospital Uganda identified Hb FS in 3.9% of newborns,³² but a more recent nationally representative sample identified the highest prevalence nationally to be 1.5% in the East-Central areas of the country.³³ One study reported a higher prevalence of 2.4% among a smaller sample of newborns at a single center in southern Nigeria.³⁴

The high prevalence of hemoglobinopathies in Northwestern Tanzania establishes SCD and other hemoglobinopathies as problems of major public health importance that must be addressed if improvements in child survival are to be achieved. If limited funding to address SCD is available to address this threat, policies for prevention and management of SCD through screening and early preventive care ought to be established first in areas of highest prevalence. Newborn screening programs are among the most cost effective.^{35,36} They provide the opportunity for parental education regarding care of the affected child as well as communication regarding the risk of future conceptions being affected. It also allows mothers who were previously undiagnosed to establish care for their own SCD.

The most important hematological changes over the course of follow-up in this study were the hemoglobin and RDW. At birth, the neonates with sickle cell anemia had normal red blood cell indices because of the impact of fetal hemoglobin. However, at 3 months, infants with sickle cell anemia had a pronounced drop in their hemoglobin and increase in RDW. This is expected as the neonates with Hb FS are undergoing an increased rate of hemolysis as they lose fetal hemoglobin and increase the percent of abnormal beta globin. Subsequent hemolysis due to the polymerization of hemoglobin and deformation of the red blood cell shortens the half-life of sickled cells to 10–20 days.^{7,31,37} Our study confirms that this change in hematological profile occurs as early as 3 months of age even in the absence of the clinical phenotypic changes associated with sickle cell anemia such as painful crises or dactylitis. These findings confirm observations in other studies and suggest that a pronounced anemia in neonates should prompt further investigations, especially when hemoglobinopathies are suspected.³⁸

Our study had several limitations. While a few clinical complications due to hemoglobin variants in children may be present before 6 months of age, most of the complications appear after 6 months. Because children with fever often reported to hospitals other than the study site, we were unable to determine the cause of fever in children with sickle cell anemia. A longitudinal study is needed to establish the effect of hemoglobinopathies in children in SSA. HPLC is a promising diagnostic tool as an initial screening method of hemoglobin variants and is useful at detecting variants, but some rare variants could have been missed on HPLC that would have been detected on capillary electrophoresis. Using the peak in the A₂ window from HPLC to diagnose β^+ -thalassemia is an inaccurate technique and requires supplementary data (e.g., family studies, RBC indices, and capillary electrophoresis) to confirm the diagnosis. Abnormal hemoglobins in our study were not confirmed with a second modality.

5 Conclusion

The prevalence of SCD in Northwestern Tanzania is one of the highest in the world. This degree of disease would make newborn screening and a comprehensive care package cost effective. Future health policies should provide funding for SCD and hemoglobin variant programs, and establish comprehensive care programs for prevention and management of complications, caregiver education, and nutrition for improved awareness of the disease process in the community. This could significantly decrease the morbidity and mortality associated with SCD in Northwestern Tanzania.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CBC	complete blood count
HPLC	high-performance liquid chromatography
LTFU	loss to follow-up
RDW	red cell distribution width
SCD	sickle cell disease
SCT	sickle cell trait
SSA	sub-Saharan Africa

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Figure 1.

Map of Tanzania. Regions served by Bugando Medical Centre and Sekou Toure Referral Hospital outlined in green. Derived from http://commons.wikimedia.org/wiki/File:Tanzania_location_map.svg © Sémhur/Wikimedia Commons/CC-BY-SA-3.0 (or Free Art License)

Key: BMC=Bugando Medical Centre, CBC=complete blood count, Hb=haemoglobin, HPLC=high performance liquid chromatography, LTFU=lost to follow up, STH=Sekou Toure Hospital

Figure 2.

Flow chart of neonates enrolled from August 2014 to September 2014 and those selected for follow-up at 3 months and 6 months

* FAS represent those with sickle trait or those with sickle- β^+ thalassemia

** FS represent those with sickle cell anemia or those with sickle- β^0 thalassemia

Figure 3.

Prevalence of hemoglobinopathies in 919 neonates screened from August to September 2014 at Bugando Medical Centre and Sekou Toure Referral Hospital, Mwanza, Tanzania

Figure 4.
Change in mean hemoglobin over the first 6 months of life compared between those with normal hemoglobin (Hb FA), sickle cell trait (Hb FAS), and sickle cell anaemia (Hb FS)

Table 1

Baseline characteristics of 919 neonates screened for hemoglobinopathies at Bugando Medical Centre and Sekou Toure Hospital from August 2014 to September 2014

Characteristic	Number (%) or median (interquartile range)
Age (days)	2 ⁽¹⁻²⁾
Male	486 (52.9%)
Premature (<37 weeks gestation)	24 (8.9%)
Neonates' HIV status	
Exposed	58 (6.3%)
Unexposed	730 (79.4%)
Unknown	131 (14.3%)
Delivery place	
Bugando Medical Centre	430 (46.8%)
Sekou Toure Hospital	477 (51.9%)
Other	12 (1.3%)
Home region	
Mwanza	870 (94.8%)
Outside Mwanza	49 (5.2%)
Mother's education	
Never attended	53 (5.8%)
Attended primary	585 (63.7%)
Attended secondary	233 (25.4%)
Attended university	48 (5.2%)
Father's education	
Never attended	19 (2.01%)
Attended primary	459 (50.0%)
Attended secondary	369 (40.2%)
Attended university	72 (7.8%)
Family history	
Parents' sickle cell status known	12 (1.3%)
Sibling death from SCD/thalassemia	2 (0.2%)
Sibling with recurrent transfusion	18 (2.0%)
Sibling with recurrent jaundice	16 (1.7%)
Mother ill during pregnancy	86 (9.4%)
General condition	
Normal activity	874 (95.2%)
Reduced activity	20 (2.2%)
Ill appearing	25 (2.7%)
Weight	
Underweight (<2.5 kg)	75 (8.1%)
Normal (2.5–3.5 kg)	586 (63.8%)
Overweight (>3.5 kg)	258 (28.1%)

Characteristic	Number (%) or median (interquartile range)
Vital sign abnormalities	
Fever (>38.0°C)	36 (3.9%)
Tachypnea (>60 breath/min)	159 (17.3%)
Hypoxic (SpO ₂ <90% in room air)	94 (10.2%)
Bradycardia (<100/min)	223 (24.3%)
Tachycardia (>160/min)	21 (2.3%)
Physical exam	
Jaundice	14 (1.5%)
Pallor	13 (1.4%)
Splenomegaly	4 (0.4%)
Congenital abnormalities ^a	27 (2.9%)

^aHydrocephalus, spina bifida, and trisomy 21.

Table 2

Comparison of hematological parameters between different hemoglobin variants over the first 6 months of life

Variable Baseline	Hb FA n = 686	Hb FAS/FAD n = 162	P-value FA vs. FAS	Hb FS n = 13	P-value FA vs. FS	P-value All Groups
Hb F (%) ^a	76.3 ± 10.3	77.6 ± 11.5	0.003	84.7 ± 3.1	0.003	<0.001
RBC (×10 ⁶ /mm ³)	5.06 ± 0.95	5.13 ± 0.98	0.45	5.29 ± 0.88	0.42	0.56
HGB (g/dl)	16.7 ± 3.6	16.8 ± 3.1	0.68	17.7 ± 2.1	0.34	0.58
HCT (%)	50.2 ± 10.8	50.6 ± 9.1	0.73	53.4 ± 9.1	0.29	0.52
MCV (μm ³)	100.7 ± 9.5	99.1 ± 9.4	0.01	101.8 ± 7.4	0.67	0.04
MCH (pg)	33.0 ± 5.2	32.9 ± 3.2	0.03	33.7 ± 3.1	0.71	0.08
MCHC (g/dl)	32.6 ± 4.5	33.0 ± 2.7	0.14	33.1 ± 1.1	0.94	0.34
RDW (%)	9.7 ± 3.0	10.0 ± 1.1	<0.001	10.0 ± 0.8	0.11	<0.001
PLT (×10 ³ /mm ³)	222 ± 113	232 ± 129	0.54	272 ± 151	0.22	0.41
WBC (×10 ⁹ /l)	12.7 ± 11.1	12.2 ± 8.9	0.98	5.88 ± 5.84	0.005	0.019
3 Months	n = 55	n = 62		n = 10		
Hb F (%) ^a	34.9 ± 18.7	31.1 ± 14.8	0.54	61.2 ± 22.3	0.001	<0.001
RBC (×10 ⁶ /mm ³)	4.09 ± 0.80	4.15 ± 0.54	0.96	3.42 ± 0.53	0.002	0.004
HGB (g/dl)	10.2 ± 1.7	10.0 ± 1.2	0.67	8.62 ± 2.18	0.045	0.11
HCT (%)	34.8 ± 0.1	34.2 ± 3.4	0.21	29.0 ± 5.9	0.008	0.01
RDW (%)	16.5 ± 3.1	15.8 ± 0.4	0.21	20.9 ± 3.7	0.001	0.002
PLT (×10 ³ /mm ³)	423 ± 157	436 ± 152	0.35	419 ± 134	0.67	0.64
WBC (×10 ⁹ /l)	17.6 ± 22.7	12.2 ± 12.5	0.93	9.36 ± 3.77	0.90	0.99
6 Months	n = 44	n = 50		n = 8		
RBC (×10 ⁶ /mm ³)	4.27 ± 1.36	4.11 ± 1.51	0.77	4.42 ± 0.78	0.82	0.84
HGB (g/dl)	10.4 ± 6.9	9.56 ± 1.88	0.51	7.99 ± 1.15	0.016	0.017
HCT (%)	29.4 ± 8.2	30.1 ± 7.8	0.91	29.0 ± 4.7	0.33	0.55
RDW (%)	15.3 ± 5.7	16.1 ± 3.7	0.18	18.3 ± 4.0	0.003	0.11
PLT (×10 ³ /mm ³)	558 ± 563	493 ± 620	0.37	307 ± 176	0.09	0.19
WBC (×10 ⁹ /l)	8.25 ± 3.73	7.37 ± 3.38	0.29	6.99 ± 3.31	0.54	0.54

^aAt baseline, Hb F was available for all 919 participants (722 FA, 182 FAS and FAD, 13 FS, 2B⁺) and at 3-month follow-up Hb F was available for 68 (21 FA, 37 FAS and FAD, 10 FS).

Significant *P*-values are written in bold.

MCV, mean corpuscular volume.