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Sickle cell disease and severity of anemia in a low-resource city: assessing functional capacity by six-minute walk test

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Abstract

Background:

In low-resource settings, homozygous sickle cell disease (SCD) is characterised by severe anaemia and growth retardation, making the assessment of functional capacity a significant clinical challenge for patient follow-up.

Methods:

This cross-sectional analytical study compared 112 SCD patients with 112 healthy controls (aged 5–25 years) using the six-minute walk test (6MWT). Performance was normalised as a percentage of the predicted theoretical distance (%PTD) using Geiger's equations, while monitoring oxygen saturation and heart rate.

Results:

Patients exhibited severe anaemia (7.0 ± 1.0 vs. 12 ± 1.0 g/dL, $p < 0.0001$) and major growth retardation (93% vs. 29%, $p < 0.0001$). The mean distance covered was significantly lower in patients (250 ± 40 m) than in controls (332 ± 65 m; $p < 0.001$); after normalisation, patients achieved only 57% of their predicted capacity compared to 74% in controls. Significant exercise-induced desaturation and delayed recovery were observed. Regression analysis demonstrated that anaemia was the strongest independent predictor of reduced functional capacity ($\beta = -74$, $p < 0.001$; $R^2 = 0.38$), whereas growth retardation was not a significant factor.

Conclusions :

SCD severely impairs functional capacity, independently of growth retardation. Anemia emerges as the primary factor limiting physical performance, highlighting the importance of its management in improving patient autonomy. In low-resource settings, 6MWT provides a robust and accessible clinical tool for assessing disease severity.

1. Introduction

Sickle cell disease (SCD), a genetic hemoglobin disorder, remains particularly prevalent in sub-Saharan Africa, where it represents a major cause of morbidity and mortality among young adults [1]. In this region, the incidence rate at birth is estimated between 1% and 2%, placing sub-Saharan Africa at the forefront globally in terms of impact. After Nigeria, the Democratic Republic of Congo (DRC) ranks second in the number of newborns affected by SCD [1, 2]. With a population of approximately 111 million, the DRC records between 25% and 30% individuals heterozygotes for HbS, and 2% to 3% of

affected newborns, i.e. approximately 40,000 cases annually [3]. In the absence of major intervention strategies, the prevalence of this condition tends to increase [4, 5]. In the DRC, the current population is 105.789.731 as of 2023 with a projected increase of 110% to 218.246.072 by 2050 [6]. This projection for 2050 also predicts a worst-case scenario for SCD in the DRC if no serious measures are taken to manage the disease through concrete actions at the local level.

Despite its scale, SCD remains largely underdiagnosed, contributing to increased mortality and morbidity [7]. This disease is characterised by vaso-occlusive crises, chronic anemia, and multi-systemic involvement, significantly impairing patients' functional capacity [8–10]. The progression of SCD leads to a decline in physical health, reducing autonomy and complicating social integration [11].

Despite therapeutic advances, cardiorespiratory complications remain the leading cause of mortality in Africa. This burden is exacerbated by the absence of formalised recommendations, resulting in a paucity of consolidated longitudinal data [12]. Patients commonly exhibit exertional intolerance and reduced physical performance, primarily attributable to anemia [13].

In this context, the six-minute walk test (6MWT) is an internationally recognised tool for assessing cardiorespiratory endurance and overall physical performance [14]. Its use in SCD patients helps to objectify functional reserve, which is often impaired [15, 16]. However, the literature remains limited regarding the assessment of the relationship between performance on the 6MWT and tolerance to anemia in Africa.

The present study aims to analyse the correlation between 6MWT performance and anemia in SCD patients living in Mbujimayi, DRC. Specifically, it seeks to evaluate functional capacity of these patients in the context of daily activities, to better characterize adaptative response to anemia, and to optimise patient management.

2. Materials and Methods

2.1. Type and setting of the study

This was a cross-sectional, analytical and comparative study conducted at the pediatric clinic of Mbujimayi in the city of Mbujimayi, DRC, characterised by a resource-limited context[17]. The study compared a population of sickle cell patients (homozygotes for hemoglobin S) with a control group consisting of healthy subjects. The study was conducted over a period of 12 months (January – December 2024).

2.2. Study population and sampling

A total of 224 participants were included in the study. The cohort was evenly divided into two groups comprising 112 SCD patients (cases) and 112 control subjects (Fig. 1). Inclusion criteria for the case group were a confirmed diagnosis of SCD by hemoglobin electrophoresis, clinical steady state, age between 5 and 25 years, and signed informed consent from the patient or legal representative. The

control group consisted of healthy subjects matched by living environment. Exclusion criteria comprised comorbid cardiac or pulmonary diseases, active acute complications, prior history of stroke or leg ulcers, presence of fever, and pre-test reports of abnormal fatigue.

2.3. Data collection and biological measurements

Data were collected quarterly during follow-up consultations, using individual forms, then consolidated into an Excel database. For each participant, anthropometric data (weight, height), demographic data (age, gender) was collected via a structured questionnaire. Clinical data (weight, height, heart rate, and oxygen saturation) were obtained during the medical consultation. A blood sample was taken to determine hemoglobin (Hb) level using hematology analyser (URIT 3020 Haematology Analyser, 3-part, URIT Medical Electronic Co., Ltd, Guili, Guangxi 541004, P.R. China). Anemia was defined according to WHO thresholds adjusted for age [18].

2.4. Operational definitions

Anemia: It is determined by a hemoglobin (Hb) level below the reference thresholds, according to age and sex.

Heart Rate (HR): It is recorded at rest, every minute where possible, and at the end of the exercise to assess the cardiovascular response to exertion.

Oxygen Saturation (SpO2): Exertional desaturation is monitored using a pulse oximeter.

Growth retardation: This term refers to a body weight significantly lower than the established references for age and sex; it is generally defined as being below the 3rd percentile (or < -2 standard deviations) on the WHO growth charts for children.

6-Minute Walk Distance (6MWD): This is the primary endpoint, measured in meters.

Recovery: The time required for HR and SpO2 to return to baseline values.

Total Distance Covered: This value corresponds to the sum of the completed laps and the final distance recorded when the timer is stopped.

2.5. Functional capacity assessment (6MWT) [19]

Functional capacity was assessed by the Six-Minute Walk Test (6MWT), conducted in accordance with the recommendations of the American Thoracic Society (ATS) [20] following the standard protocol [15]. Explanations on the overall procedure, precautions, possibilities of interrupting the test, and expected results were given to each participant individually and in the local language. In brief, participants were asked to walk the greatest possible distance in six minutes on a flat, marked course., while the distance

covered is recorded. It was carried out in a controlled environment, with trained personnel to ensure safety. Patients were asked to perform the test after a 20-minute rest. In the event of signs of distress (severe dyspnoea, chest pain, extreme fatigue), the test was interrupted in accordance with the recommendations. Refreshments and a snack were provided to each participant before and after the test. Transcutaneous arterial oxygen saturation was measured using pulse oximetry (BCI International, Waukesha, Wisconsin, USA). Heart rate and perceived exertion were also recorded for each participant. Vital signs were assessed at baseline and every two minutes during the test. Participants were continuously accompanied throughout the test by a physiotherapist or a physician carrying the pulse oximeter. For children under 10 years of age, the test was conducted in the presence of the legal representative.

2.6. Data normalisation

2.6.1. Predicted Theoretical Distance

To account for potential bias related to growth differences (weight, height) between groups, the predicted theoretical distance (PTD) was calculated for each participant using the reference equations of Geiger et al.[21, 22] :

- • Male = [7.57 x height (cm)] - [1.76 x weight (kg)] – [5.02 x age (years)] – 309
- • Female = [2.11 x height (cm)] – [2.29 x weight (kg)] – [5.78 x age (years)] + 667

Lower Limit of Normality (LLN):

- • Male = Theoretical normal distance − 153 metres
- • Female = Theoretical normal distance – 139 metres

Physical performance was then expressed as percentage of the predicted distance (%PD) according to the following formula:

%PD = (Real Distance covered/ Lower Limit of Normality) X 100

2.6.2. Hemoglobin Level Normalization

To standardize biological data across the cohort and account for physiological disparities related to sex and age, hemoglobin (Hb) levels were converted into a percentage of the expected normal value.

The normalized hemoglobin level (Hbnorm) was calculated using the following formula:

• Hb_{norm} (%) = (Hb patient/Hb lower reference value) x 100

The reference values were based on the lower reference value of the range defined by the World Health Organization (WHO):

- • 3–5 years : Hb: 11–14 g/dL

- • 6–12 years : Hb: 11.5–15 g/dL
- • 12 years : Hb: 12–16 g/dL

This normalization process allows for an assessment of the relative oxygen-carrying capacity deficit. It further facilitates correlation analyses with functional parameters from the 6-minute walk test (6MWT), specifically total distance walked and exertional desaturation.

2.7. Statistical Analysis

The data were entered into Epi-Info version 7.2.6.0.

1. 1. Descriptive analysis: Continuous variables were expressed as mean ± standard deviation (SD) after normality was assessed using the Shapiro-Wilk test.
2. 2. Comparisons: Student's t-test (for equal variances, verified by Bartlett's test) and the Mann-Whitney/Wilcoxon test were used to compare mean distance and hemoglobin levels between the two groups.
3. 3. Correlation and regression analysis: Simple linear regression was performed to evaluate the impact of hemoglobin levels on the percentage of distance covered. The strength of the association was measured by the coefficient of determination (R^2).

Statistical significance was set at $p < 0.05$.

3. Results

3.1. Description of the study population

Socio-demographic and biological characteristics of the study population are summarized in Table 1. Although both groups were matched by living environment, significant disparities were observed regarding nutritional status and hematological parameters. Notably, SCD patients presented with severe anemia, with a mean hemoglobin level of 7 ± 1.0 g/dL compared to 12.0 ± 2.0 g/dL in controls ($p < 0.0001$). The analysis of normalized hemoglobin levels (Hb_{norm}), expressed as a percentage of the expected value for age and sex, reveals a major disparity between the two groups ($p < 0,001$). Sickle cell patients exhibited a mean hemoglobin level of 61% ± 10 of the physiological norm, with values ranging from 39% to 85%. In comparison, the control group showed a mean of 104% ± 18. The mean difference of 43% (95% CI: [40–48]) between the two groups underscores the severity of the chronic oxygen-carrying capacity deficit in the SCD subjects within this cohort.

Table 1
Characteristics of the cohort

Parameters		**SCD Patients (n = 112)**	**Controls n = 112)**	**p-value**
Age (years)				
	Mean (± SD)	11 (± 5)	10 (± 6)	0.006
Age categories (based on Hb norms)				
	3–5 years (Ref Hb: 11–14 g/dL), n (%)	14 (26)	39 (74)	< 0.001
	6–12 years (Ref Hb: 11.5–15 g/dL), n (%)	46 (52)	43 (48)	
	> 12 years (Ref Hb: 12–16 g/dL), n (%)	52 (63)	30 (37)	
Sex				
	Male, n (%)	51 (46)	60 (54)	n.s.
	Female, n (%)	61 (54)	52 (46)	
Hemoglobin level				
	Hb : Mean (± SD) g/dL	7 (± 1)	12 (± 2)	< 0.001
	Hb_{norm} : **Mean** (± SD) (%)	61 (± 10)	104 (± 18)	< 0.001
Anemia				
	Yes, n (%)	112 (100)	44 (39)	< 0.001*
	No, n (%)	0 (0)	68 (61)	
Growth retardation				
	Yes, n (%)	104 (93)	32 (29)	< 0.001
	No, n (%)	8 (7)	80 (71)	
Hb_{norm} :Normalised Hemoglobin, Hb : Hemoglobin. *RR = 3.54; 95% CI: [2.76–4.55].				

In accordance with WHO thresholds, the prevalence of anemia was 100% (n = 112) among patients, compared to 39% (n = 44) in thecontrol group. Risk analysis demonstrated that subjects in the "Patient" group were 3.5 times more likely to present with anemia than control subjects (RR = 3.54; 95% CI: [2.76–4.55]; p < 0.0001).

Furthermore, growth retardation was almost systematic among patients (93%) vs (29%) in control group, highlighting the constitutional impact of the disease in this limited-resource setting

3.2. Walk distance progression by intervals during the 6MWT

Analysis of walk distance kinetics by intervals (Table 2) showed a significant difference between the two groups starting from the first two-minute interval (80 ± 18 m for patients vs. 108 ± 29 m for controls; $p < 0.001$). At the fourth minute, the cumulative distance was 161 ± 28 m in SCD patients and 217 ± 48 m in controls ($p < 0.001$). At the end of the test (6 minutes), the mean total distance covered by SCD patients was 250.0 ± 40.5 meters, compared to 331.9 ± 65.2 meters for controls ($p < 0.001$). The mean difference in total distance between the two groups was 81.9 meters. The variances of the distances covered were significantly heterogeneous between the two populations (Bartlett's test, $p < 0.0001$).

Table 2
Cumulative walk distance progression during the 6MWT

Parameters	**SCD Patients (n = 112)**	**Controls (n = 112)**	**p-value**
Cumulative distance (m)			
At 2 minutes (Mean ± SD), m	80 ± 18	108 ± 29	< 0.001
At 4 minutes (Mean ± SD), m	161 ± 28	217 ± 48	< 0.001
At 6 minutes (Mean ± SD), m	250 ± 40	332 ± 65	< 0.001
TDC			
TDC < LLN, n (%)	100 (89)	78 (70)	< 0.001*
TDC > LLN, n (%)	12 (11)	34 (30)	
m= meter, TDC: Total distance covered, LLN: Lower Limit of Normal.			
* Yates-corrected $X^2 = 12.06$; $p = 0.0005$. Odds Ratio 0.27 (95% CI: 0.13–0.56).			

Analysis of the 6-minute walk test performance reveals a significant disparity between the two groups regarding the attainment of the Lower Limit of Normal (LLN). In the overall cohort (N = 224), only 20.54% (n = 46) of subjects reached or exceeded the LLN. This performance was markedly higher in the Control group (30.36%) compared to the Patient group (10.71%). Conversely, the vast majority of patients (89.29%) exhibited a pathological walking distance, falling below their calculated LLN. Statistical analysis confirms that 'Patient' status is strongly associated with the failure to reach the LLN (Yates-corrected X2 = 12.06; p = 0.0005). Patients showed a significantly lower probability of achieving a normalized result compared to control subjects, with an Odds Ratio (OR) of 0.27 (95% CI: 0.13–0.56).

3.3. Evolution of physiological parameters during exercise

Regarding the evolution of heart rate and oxygen saturation during exercise, changes in pulse oxygen saturation (SpO2) during the walk test are presented in Table 3. At rest, SCD patients exhibited significantly lower oxygen saturation compared with controls (94 ± 3.0% vs. 97 ± 2.0%; p < 0.001). This difference became more pronounced during exercise: at the four th minute, mean SpO2 in patients decreased to 91 ± 8.4% (Fig. 2), whereas it remained relatively stable at 95 ± 4.2% in controls (p < 0.001). At the end of the effort (6 minutes), persistent desaturation was observed in SCD patients, with a mean value of 92 ± 7.3%, compared with 95 ± 4.7% for controls (p < 0.001). Variability in oxygen saturation was notably greater in SCD patients, particularly at the fourth minute of the test.

Table 3
Oxygen saturation (SpO2) evolution during exercise

Monitoring interval	**SCD Patients (n = 112)**	**Controls (n = 112)**	**p-value**
SpO2 at baseline (Rest), %	94 ± 3.0	97 ± 2.0	< 0.001
SpO2 at 2 minutes, %	92 ± 7.2	96 ± 2.0	< 0.001
SpO2 at 4 minutes, %	91 ± 8.4	95 ± 4.2	< 0.001
SpO2 at end of test (6 minutes), %	92 ± 7.3	95 ± 4.7	< 0.001
SpO2 variability (4th min)	Marked variability	Stable	< 0.001

The evolution of heart rate (HR) during the exercise test is presented in Table 4. A significant difference between the two groups was observed at each time point. At the second minute, mean HR was 113 ± 16 bpm in SCD patients versus 123 ± 16 bpm in controls (p < 0.001). This pattern persisted at the fourth minute (114 ± 14 bpm vs. 119 ± 23 bpm; p = 0.022) and at the end of the six-minute test, where SCD had a mean HR of 111 ± 16 bpm compared with 123 ± 23 bpm in controls (p < 0.001). Unlike controls, SCD patients demonstrated relative stability, or even a slight decrease, in mean HR between the second and sixth minutes of exercise.

Table 4
Heart rate (HR) evolution during the exercise test

Monitoring Interval	**SCD Patients (n = 112)**	**Controls (n = 112)**	**p-value***
Baseline HR (Rest), bpm	98 ± 12	82 ± 10	< 0.001
HR at 2 minutes, bpm	113 ± 16	123 ± 16	< 0.001
HR at 4 minutes, bpm	114 ± 14	119 ± 23	0.022
HR at the end of test (6 minutes), bpm	111 ± 16	123 ± 23	< 0.001
HR Trend (2 to 6 min)	Stability / Slight decrease	Progressive increase	< 0.001
*p-value derived from the Mann-Whitney test (preferred due to heterogeneous variances confirmed by Bartlett's test, p < 0.05 for HR at 4 and 6 min. bpm = beats per minute, HR = Heart rate.			

3.4. Relative functional capacity (Predicted theoretical distance)

Analysis of normalized functional capacity, expressed as the percentage of the predicted theoretical distance (Geiger equation), reveals a significant impairment in SCD patients compared controls (Fig. 3). Controls showed a mean performance of 74 ± 43%. In contrast, SCD patients displayed a significantly lower mean functional capacity of 57 ± 39%. The mean performance difference between the two groups was 17% (95% CI: 5.8–28), and highly statistically significant (p = 0.0001). Given the data distribution, the Mann-Whitney non-parametric test confirms this disparity with even greater significance (p < 0.0001). The median performance in SCD patients was only 43% [IQR: 36–68], compared to 60% [IQR: 49–84] in controls (Table 5).

Table 5
Relative functional capacity (Percentage of predicted theoretical distance)

Parameters	**SCD Patients (n = 112)**	**Controls (n = 112)**	**p-value***
Functional Capacity (%)			
Mean ± SD	57 ± 39%	74 ± 43%.	< 0.001
Median [IQR]	43% [36–68]	61% [49–84]	< 0.001
Performance Gap (%)			
Mean difference SCD versus Controls	-17		
95% Confidence Interval	[5.8–28]		
Ref= reference group			

3.5. HR and SpO2 recovery time

Recovery parameters after exercise are detailed in Table 6. A highly significant difference was observed between the two groups in the time required to return to baseline values. Mean HR recovery time was 93 ± 63 minutes in SCD patients, compared with 47 ± 36 minutes in controls (p < 0.001). Similarly, recovery of baseline oxygen saturation was markedly prolonged in SCD patients, with a mean time of 142 ± 140 minutes versus 54 ± 54 minutes in controls (p < 0.001). Sickle cell patients exhibited prolonged post-exercise physiological stress, with a median SpO_2 recovery time of 80 minutes [IQR: 20–180], nearly double that of the control group (43 minutes [IQR: 20–66].

Table 6
Exercise recovery parameters of the study population

Recovery Parameters	Statistical Parameters	SCD Patients (n = 112)	Controls (n = 112)	p-value*
Return to baseline HR (min)	Mean ± SD (min)	93 ± 63	47 ± 36	< 0.001
	Median [IQR] (min)	75 [45–120]	41 [20–60]	
Return to baseline SpO2 (min)	Mean ± SD (min)	142 ± 140	54 ± 54	< 0.001
	Median [IQR] (min)	80 [20–180]	43 [20–66]	
Oxygen debt (Δ SpO2 1 min)	Mean ± SD (min)	-	-	
	Median [IQR] (min)	-	-	

HR : heart rate, SpO2: oxygen saturation, SD: standard deviation, IQR: inter quartile range, SCD: sickle cell disease

3.6. Correlation between anemia and walk test performance

Multiple linear regression analysis (R2 = 0.38) revealed that anemia was the strongest independent predictor of the 6MWT distance (Table 7). After adjusting for age and growth parameters, patients with anemia walked 74 meters less than those without anemia (p < 0.001). Age also significantly influenced the distance covered, with an increase of 1.96 meters per year (p = 0.005). Notably, growth retardation was not significantly associated with functional capacity when anemia and age were included in the model (p = 0.106).

Table 7
Multiple linear regression analysis of factors associated with 6MWT distance.

Variable	Coefficient (β)	Std. Error	F-test	P-value
Anemia (Yes)	-74.02	9.1	66	**< 0.001**
Age (years)	+ 1.96	0.7	7.8	**0.006**
Growth retardation (Yes)	-15.17	9.4	2.6	0.107
Constant	*322.19*	*9.0*	*1267*	*< 0.001*
Note: R^2 = 0.38				

4. Discussion

This study assessed the 6MWT in SCD patients, not on hydroxyurea therapy, in a remote region of a low-resource country, a population often underrepresented in the international literature. The aim was to analyse the functional capacity of children with SCD during daily activities, independently of total hemoglobin levels, to better understand their adaptation to chronic anemia.

4.1. Hematological profile and severity of anemia

The mean hemoglobin level observed in our patients (7.0 ± 1.0 g/dL, corresponding to 61% of the physiological norm) is consistent with existing literature from Sub-Saharan Africa (SSA). This finding is in agreement with averages hemoglobin levels reported in several studies conducted in sub-Saharan Africa (SSA), including 7.0 g/dL in DRC, 7.7 g/dL in Benin, and 8.0 g/dL in a multicenter study across six SSA countries, respectively [24–26]. Those findings highlight the phenotypic severity of sickle cell disease in resource-limited settings.

Those mean hemoglobin level are markedly lower than those observed in American or European cohorts [26], where Hb levels typically range between 8.5 and 10 g/dL. It is largely due to the availability of recognized therapeutic options such as hydroxyurea or chronic exchange transfusion programs. In our cohort, this profound anemia together with near-systematic growth retardation (93%), likely contributes to the pathophysiological basis of the exercise intolerance observed during the six-minute walk test.

Furthermore, anemia was identified in nearly 40% of the control subjects (mean: 104.5%). This 'residual' anemia among the controls reflects the epidemiological realities of the Kasai region, where endemic malaria and nutritional deficiencies significantly impact the hematological parameters of the general population[27, 28]. Given these physiological constraints, it is expected that severely reduced hemoglobin levels would lead to a proportional reduce in walking distance.

4.2. Functional capacity and 6-minute walk test performance

The impairment of functional capacity observed in our study is substantial, with a mean total distance of 250 ± 40 meters in SCD patients, representing a deficit of over 80 meters compared to controls. This performance is lower than the distances reported among children with SCD in Belgium (551 ± 92 m) or in France (491 ± 64 m), respectively [29, 30]. The originality of our approach lies in the use of Geiger equations to normalize the results. Despite adjustement for age and anthropometric characteristics (weight and height), patients achieved only 57% of their predicted theoretical distance, whereas in the Belgium study, SCD children reached 86% of the predicted distance [29]. This finding suggests that reduced 6MWT performance may reflect an intrinsic limitation in oxygen transport capacity. In comparison, our controls achieved 73% of their predicted performance, a difference that may indicate influence of environmental factors (e.g., nutrition, sedentary lifestyle) on overall functional capacity in this population. SCD appears to impose an additional functional "surcharge" of nearly 17%. This disparity

is likely multifactorial, primarily explained by the severity of anemia in our cohort, as well as the broader impact of resource-limited settings on growth retardation.

Our findings highlight a profound impairment of functional capacity among sickle cell patients in Mbujimayi. Only 10.7% of patients reached the Lower Limit of Normal (LLN), compared to 30.4% in the control group. This marked deficit is explained by the complex pathophysiology of SCD, where chronic anemia is coupled with systemic organ damage. The low success rate among controls (30.4%) raises questions regarding the suitability of international reference equations (such as Enright & Sherrill) for the Congolese population. As observed by van Beers et al. (2014) in their research on SCD, local environmental and nutritional factors significantly influence baseline performance [31].. It is possible that the theoretical LLN is overestimated for this specific region, although the gap between patients and controls remains statistically indisputable ($p = 0.0005$).

4.3. Physiological adaptation and exercise progression

Analysis of the physiological response during exercise reveals marked cardiorespiratory maladaptation in SCD patients. In contrast to controls, who maintain stable SpO2 levels, patients exhibit progressive desaturation, reaching a mean of 91 ± 8.4% at the fourth minute. This drop in SpO2 likely reflects early depletion of oxygen delivery capacity in the context of increased muscular metabolic demand [32, 33]. The observation of extreme desaturation (as low as 53%) in some patients highlights the extent of exercise-induced hypoxemia that is a known risk factor known of post-exercise vaso-occlusive complications.

Paradoxically, HR during exercise remained significantly lower in patients than in controls (111 vs. 123 bpm at 6 min). This result suggests early functional limitation: rather than achieving maximal compensatory tachycardia, patients seem forced to reduce their walking intensity (a slowdown observed between minutes 4 and 6), potentially to prevent critical tissue hypoxia. This spontaneous "protective strategy," associated with delayed HR and SpO2 recovery, and is consistent with reduced chronotropic reserve and persistent post-exercise oxygen debt, characteristic of SCD pathophysiology in our context [34].

4.4. Determinants of physical performance: Predominant impact of anemia

Multivariate regression analysis identified anemia as the primary determinant of functional capacity in our cohort. With a coefficient of determination (R^2) of 0.38, our model indicates that more than half of the variability in walking distance is explained by anemia and growth development. In a cohort of SCD patients not on hydroxyurea, van Beers et al. (2014) [35] reported similar finding that anemia constituted the main factor limiting exercise tolerance with a R^2 of 0.36. Our findings also align with those of Connes et al.[36, 37].

Contrary to studies suggesting that growth retardation alone accounts for reduced performance in SCD patients [38], integrating weight and height into our models (via Geiger equations) demonstrated that the

severity of anemia (mean hemoglobin 7.0 ± 1.0 g/dL, representing 61% ± 10 of the physiological norm) largely outweighs anthropometric influence.. Each additional gram of hemoglobin was associated with a predictable improvement in distance covered, supporting that the 6MWT is a direct reflection of oxygen-carrying capacity. Finally, the 44% of unexplained variance suggests the involvement of additional unmeasured factors, such as cardiac function, micronutrient status, or modifying genetic factor, which warrant further investigations.

4.5. Study limitations

Despite the relevance of our findings, this study has several limitations. First, its cross-sectional design does not allow assessment of the longitudinal evolution of functional capacity or the impact of therapeutic interventions over time. Second, the absence of cardiac (echocardiography) and respiratory (spirometry) function measurements limits our comprehensive evaluation of the central mechanisms underlying exercise intolerance. Finally, although Geiger equations are validated for pediatric populations, the absence of specific reference values for the population of Mbujimayi in DRC may partly account for the relatively low performance scores observed even among controls (73%). Nevertheless, the relatively large sample size (n = 224) and the rigorous normalisation procedure strengthen the robustness of our findings.

5. Conclusions

This study identifies severe impairment of functional capacity in SCD patients in resource-limited settings, defined by reduced 6MWT distance, significant desaturation, and slow recovery, independent of growth retardation (Geiger equations). Anemia remains the main determinant of performance, though a model incorporating age and growth retardation reaches a predictive capacity of 38%. These results advocate for a holistic management of SCD that addresses both anemia and anthropometry. The 6MWT proves to be a robust and accessible functional biomarker, essential for monitoring disease severity in low-resource contexts. Considering these findings, strong advocacy toward multilateral organizations and governments is essential to ensure the availability and affordability of hydroxyurea. Such measures are critical to improving the quality of life for sickle cell patients in resource-limited settings.

Abbreviations

6MWT
Six-Minute Walk Test
bpm
Beats per minute
CI
Confidence Interval
g/dL
Grams per deciliter
Hb

Hemoglobin
Hb_{norm}
Normalized hemoglobin level
HR
Heart rate
IQR
Interquartile range
m
Meters
min
Minutes
R^2
Coefficient of determination
SCD
Sickle cell disease
SD
Standard deviation
SpO2
Peripheral oxygen saturation
SSA
Sub-Saharian Africa

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Mashi Research Centre, sickle cell disease and other red blood cell diseases/Pediatrics clinic of Mbujimayi (protocol code N/Ref: 014/CR/CRM/CPM/YMK/2024).

Clinical trial number : not applicable

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. In the case of minors, informed consent was obtained from their parents or legal guardians.

The purpose and procedures of the study were explained to the participants and legal guardians.

The participants were informed that they could withdraw at any time without further obligation and would continue to receive care without prejudice. The anonymity of the participants was guaranteed, and no personal data were recorded.

Consent for publication: Written informed consent has been obtained from the patients to publish this paper.

Availability of data and materials: All data generated and/or analyzed during this study is available in a database from the corresponding author on reasonable request.

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Figures

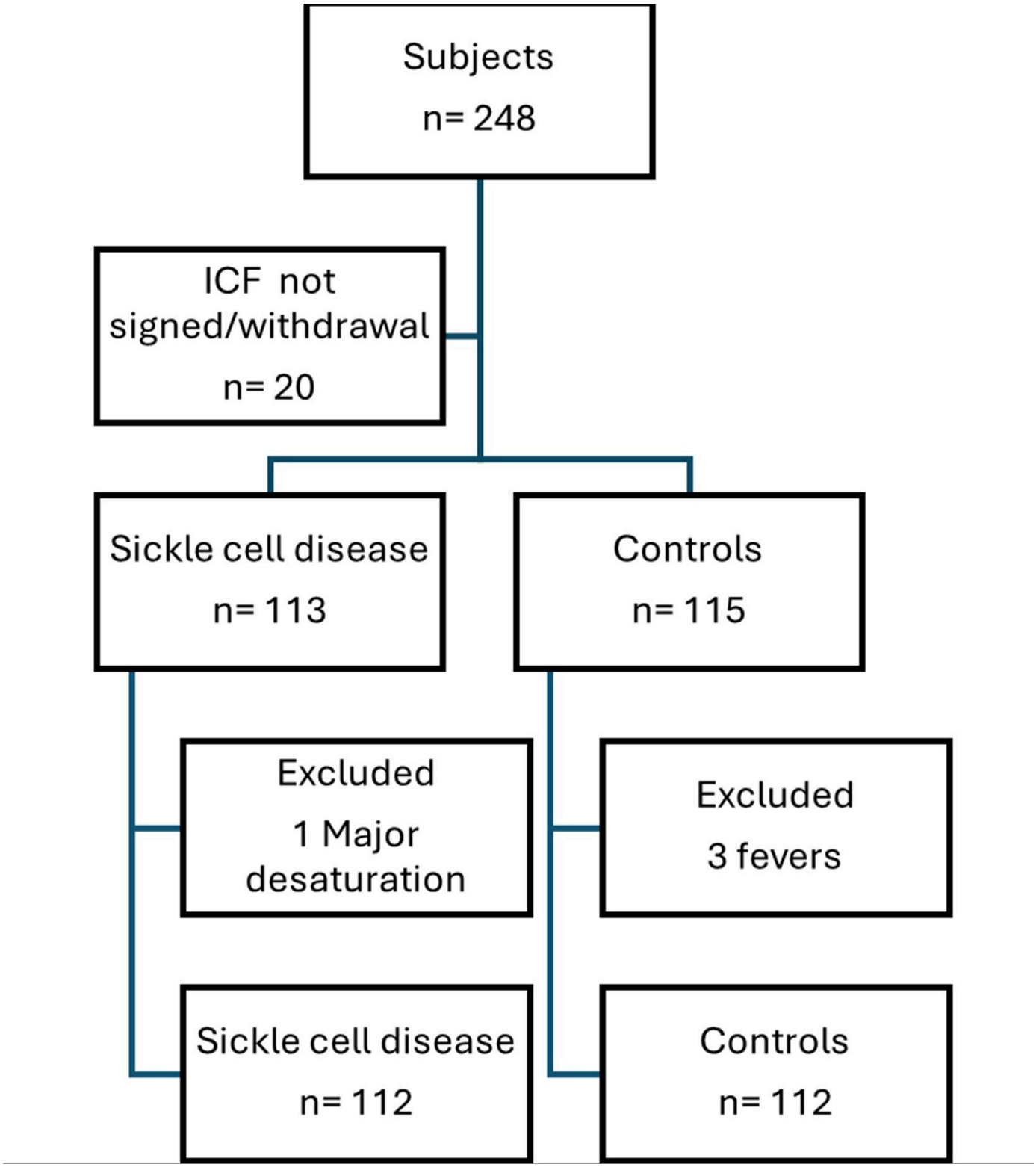


Figure 1

Participant enrollment flow diagram

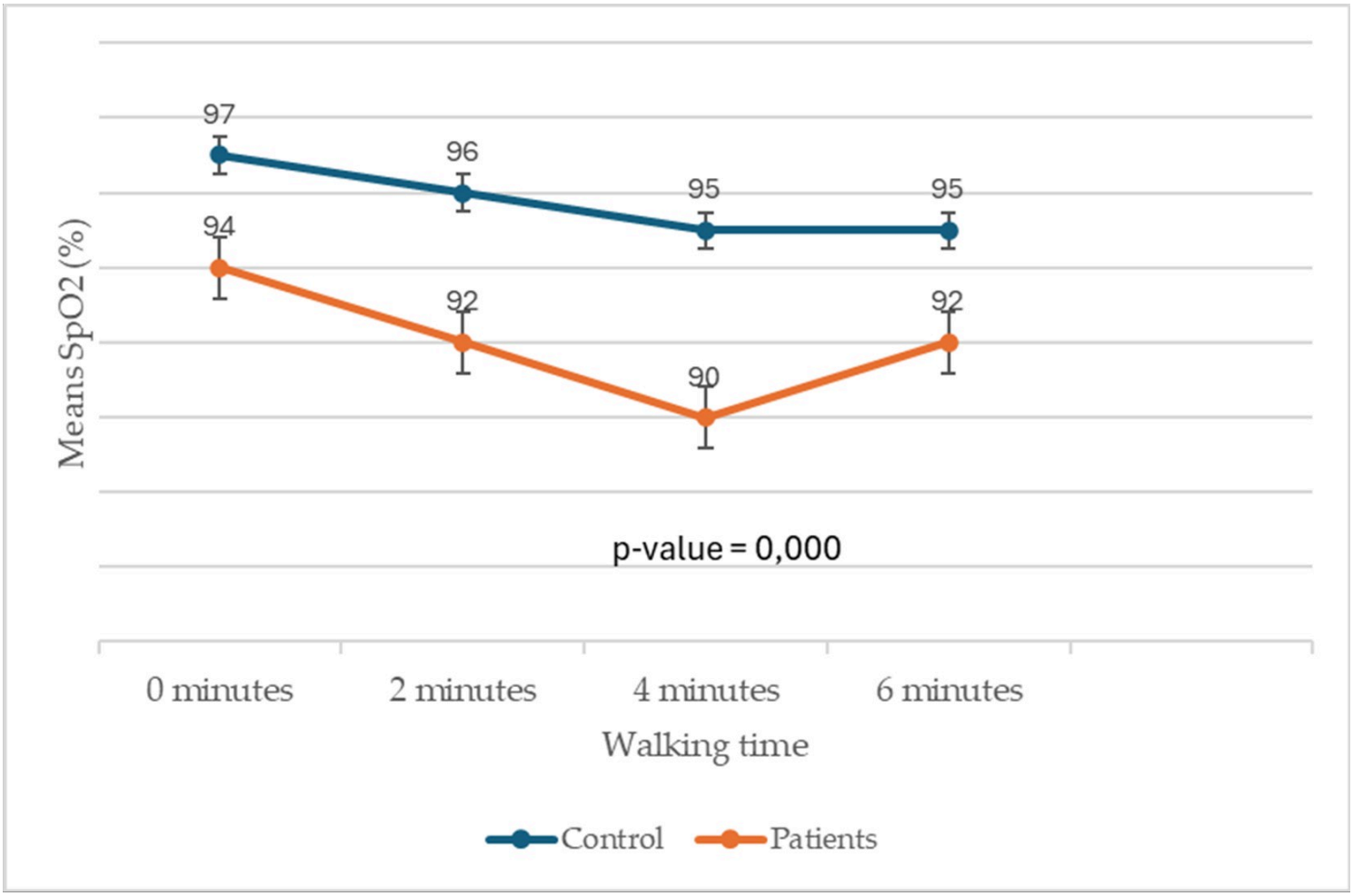


Figure 2

Mean oxygen saturation levels in SCD patients and the control group during the 6-minute walk test

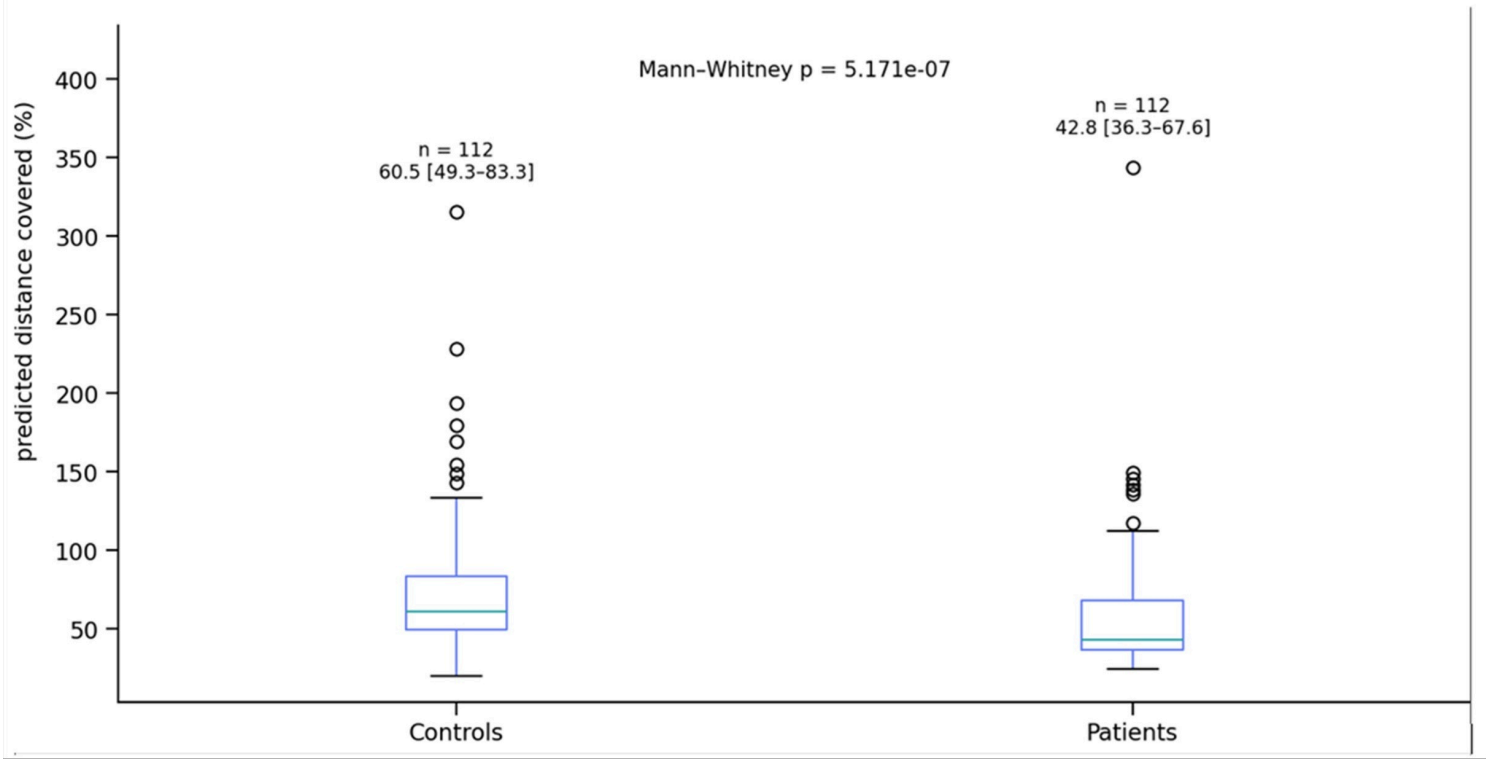


Figure 3

Predicted distance covered by control subjects and SCD patients (median).

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