Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2018, 8, 217-228
http://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

Blood Pressure Patterns and Factors Associated with Relative Hypertension among Steady State Sickle Cell Disease Patients in Kinshasa, Democratic Republic of the Congo: A Cross-Sectional Study

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How to cite this paper: Mboliasa, P.I., Lepira, F.B., Makulo, J.R., Nkodila, A., Sumaili, E.K., Bukabau, J.B., Mokoli, V.M., Longo, A.L., Zinga, C.V., Kanjingulu, F.M.P., Nlandu, Y.M., Engole, Y.M., Mukendi, M.M., Kadima, E.M., Ilunga, C.K., Ekulu, P.M. and Nseka, N.M.N. (2018) Blood Pressure Patterns and Factors Associated with Relative Hypertension among Steady State Sickle Cell Disease Patients in Kinshasa, Democratic Republic of the Congo: A Cross-Sectional Study. *World Journal of Cardiovascular Diseases*, **8**, 217-228.
https://doi.org/10.4236/wjcd.2018.83021

Received: February 6, 2018
Accepted: March 26, 2018
Published: March 29, 2018

Abstract

Background: Although systemic hypertension is rarely seen in steady state sickle cell disease (SCD), relative hypertension has been reported to be associated with an increased risk of cardiovascular and renal complications. **Objective:** To determine the prevalence of BP patterns and assess factors associated with relative hypertension in sickle cell anemia (SCA) adult patients. **Methods:** Clinical data and office BP were obtained from 103 consecutive steady-state SCA adult patients (mean age 26 ± 7.9 years, 66% females, 22.3% on hydroxyurea) attending four healthcare centers providing SCD-specific care in Kinshasa. Seated BP was measured using an automated electronic device. Three consecutive blood pressure measurements were taken with 2 minutes interval between readings and the average of the 2 last readings was considered for the analyses. Normal BP, relative hypertension and systemic hypertension were defined as BP < 120/70 mmHg, 120 - 139/70 - 89 mmHg and ≥140/90 mmHg, respectively. **Results:** Normal BP, relative hypertension and systemic hypertension were observed in 56 (54%), 43 (42%) and 4 (4%) of SCA patients, respectively. In multivariate analysis, factors associated with relative hypertension were leg ulcer (aOR 2.05; 95%CI 1.77 - 5.18; p = 0.016), central obesity (aOR 3.32; 95%CI 1.28 - 6.24; p = 0.001), smoking (aOR 5.02; 95%CI 1.51 - 9.50; p = 0.017), and microalbumiuria (aOR 3.44; 95%CI 1.44 - 5.76; p = 0.035). **Conclusion:** Relative hypertension was a common finding in

the present case series and associated with traditional cardiovascular risk factor as well as factors specific to SCD highlighting the need for measures to prevent its progression towards systemic hypertension and associated cardiovascular and renal disease.

Keywords

Relative Hypertension, Prevalence, Associated Factors, Sickle Cell Anemia, Black Africans

1. Introduction

In contrast to the general population, a seeming finding in sickle cell disease (SCD) is that patients do not usually suffer from a high prevalence of systemic hypertension in spite of extended endothelial dysfunction, chronic inflammation and vasculopathy [1] [2] [3]. However, recent data indicate that blood pressure (BP) abnormalities such as relative systemic hypertension (BP ≥ 120 - 139/70 - 89 mmHg) and increased pulse pressure (PP ≥ 60 mmHg) or systolic hypertension are associated with an increased pulmonary, renal and cardiovascular disease (CVD) risk [1] [2] [4] [5] [6]. In addition, the lack of nocturnal BP dip using ambulatory BP monitoring (ABPM), a well-known risk factor for the development and progression of renal and cardiovascular disease, has been reported to play an important role in SCD-associated target organ involvement [5]. Therefore, the assessment of office or clinic BP patterns and/or 24-hour circadian BP patterns on ABPM, especially in SCD patients with kidney involvement (e.g. microalbuminuria) could help reducing the risk of renal disease progression and CVD development.

In Democratic Republic of the Congo (DRC), the prevalence of SCD is estimated to be of 2% [7] and renal involvement in terms of microalbuminuria is a common finding [8] [9]. However, patterns of office BP as well as the prevalence and factors associated with relative hypertension in SCD patients have not yet been evaluated. We took advantage of the availability of data from a cross-sectional study of renal function in steady-state SCA adult patients to perform a post-hoc analysis on the prevalence and factors associated with relative hypertension.

2. Patients and Methods

From December 15, 2016 to March 31, 2017, a multicenter cross-sectional study was conducted on consecutive steady-state adult patients with electrophoresis diagnosis of SCD attending four healthcare centers (Centre Hospitalier Monkole/CHM, Centre d'Anémie SS Mabanga/CASM, Hôpital des Soeurs de Kingasani/HSKand Centre Saint Crispin/CSK) providing specific SCD care in Kinshasa, the capital City. Patients were asked to participate to the study on a volunteer basis. The study protocol was reviewed and approved by the Ethics Committee

of Kinshasa School of Public Health, University of Kinshasa (ESP/CE/090/2016). Clinical Steady-state was defined as the absence within the last two months prior to the study of vaso-occlusive crisis (VOC) or hemolysis, blood transfusion, acute chest syndrome, fever or any acute illness [10]. Patients with illnesses known to interfere with urinary albumin excretion such as diabetes, HIV infection, hepatitis B or C were excluded. Variables collected for each patient, based on interviews and physical examination at the time of visit and on data drawn from clinical records, were demographic (sex, age), past medical history (number of blood transfusion, pulmonary artery hypertension, vascular occlusive crisis/VOC, leg ulcer, priapism, aseptic osteonecrosis/AON, family and personal hypertension, family diabetes, stroke, hydroxyurea use, alcohol intake, smoking) and physical examination (height, weight, BP, and waist circumference). A standardized questionnaire administered by trained interviewers was used to collect medical information. Patients who smoked at least one cigarette per day at the time of consultation were classified as active smokers [11]. Excessive alcohol intake was defined by regular intake of ≥2 glasses per day of beer or equivalent for at least 1 year knowing that 1 glass of beer contain 10 g of alcohol [12]. Height and weight were measured patients without heavy garments and shoes using a wooden vertical stadiometer and SECA scale (Vogel etHalk, Hamburg, Deutschland), respectively. Body mass index (Kg/m^2) was calculated as weight (Kg) divided by (height, m^2); underweight, overweight and obesity were defined as BMI < 18.5, 18.5 - 29.9 and ≥30 Kg/m^2, respectively [13]. Waist circumference (WC) was measured to the nearest 0.1 cm at the mid-point between the lower costal margin and the level of the anterior superior iliac crest using a taperecord. Central obesity was defined as WC > 80 cm and >94 cm in women and men, respectively [14]. Seated BP measurement was taken on the left arm by a trained nurse after 5 minutes of rest, using an automated electronic sphygmomanometer OMRON HEM 907 (Omron Matsusaka Co. Ltd., Kyoto Japan). Three consecutive BP measurements were taken with 2 minutes interval between readings and the average of the 2 last readings was considered for analyses. Pulse pressure (PP, mmHg) and mean arterial BP (MAP, mmHg) were calculated as systolic blood pressure (SBP) minus diastolic BP (DBP) and DBP + PP/3, respectively. PP > 60 mmHg defined increased PP levels, a marker of arterial stiffness [15]. Normal BP, relative hypertension and systemic hypertension were defined BP < 120/70 mmHg, 120 - 139/70 - 89 mmHg and ≥140/90 mmHg, respectively [2].

A 12-hour overnight venous blood sample was obtained for each patient and processed at the Reference Laboratory of the DRC National AIDS Control Program using an automatic device for full blood count (SYSMEX XP-300, Ville, Pays), uric acid blood urea nitrogen and serum creatinine (COBAS C111). Serum uric levels > 360 μmol/l and 420 μmol/l defined hyperuricemia in women and men, respectively [16]. Renal function was evaluated by the estimation of glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology (CKD-EPI) without adjustment for ethnicity [17]. eGFR < 60 ml/min/1.73 m^2 defined reduced kidney function [17]. eGFR > 130 ml/min/1.73 m^2 and >140

ml/min/1.73 m^2 definedglomerular hyperfiltrationin women and men, respectively [18]. Urinary albumin excretion was determined in spot morning urine (DCA Vantage SYSMEX) and express as albumin creatinine ratio (ACR, mg/g). ACR 30 - 299 mg/g and ≥300 mg/g defined microalbuminuria and macroalbuminuria, respectively [19].

Statistical analyses were performed using the Statistical Package for Social Sciences (SSPS Inc, Chicago, Illinois, USA) version 17.0 software. Results are summarized as counts and percentages for qualitative variables and as mean ± standard deviation (SD) for quantitative variables. Comparisons of means of two or more than two groups and of proportions used Student t-test, one way analysis of variance (ANOVA) and chi-square test, respectively. Independent factors associated with relative hypertension were assessed using multivariate logistic regression analysis. A p-value < 0.05 defined the level of statistical significance.

3. Results

The present cross-sectional study included 103 steady state SCD adult patients of whom 66% were females (**Table 1**). Their mean age, BMI, SBP, DBP, MP and PP were 26 ± 7.9 years, 18.8 ± 2.6 Kg/m^2, 109.2 ± 13.2 mmHg, 67.6 ± 10.2 mmHg, 81.5 ± 10.1 mmHg and 41.7 ± 10.7 mmHg, respectively. The proportions of patients with previous history of leg ulcer, aseptic osteonecrosis (AON), more than 3 blood transfusions, VOCand priapism were 25.2%, 13.6%, 12.6%, 5.8% and 5.8%, respectively. Nearly 2 in 10 patients were receiving hydroxycarbamide (HU). Their mean Hb level, reticulocytes count, uric acid, eGFR (CKD-EPI) and ACR levelswere 76 ± 15 g/l, 9.6% ± 3.2%, 374.85 ± 113.05 µmol/l, and 164.7 ± 36.4 ml/min/1.73 m^2 and 38.3 ± 6.3 mg/g, respectively.

BP patterns of the study population are depicted in **Figure 1**. Normal BP, relative hypertension and systemic hypertension were observed in 56 (54%), 43

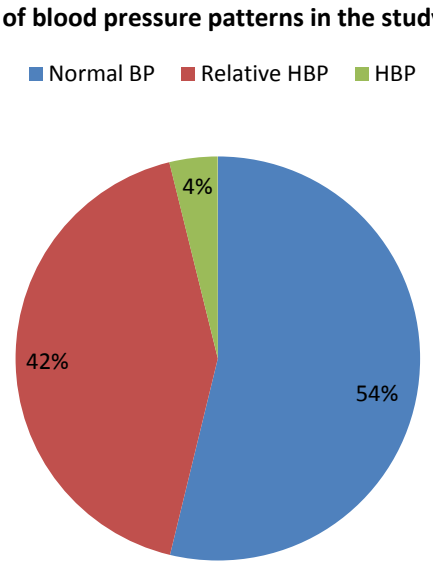

Figure 1. BP patterns of the study population.

(42%) and 4 (4%) patients, respectively. Compared to patients with normal BP (Table 1), those with relative hypertension had in average significantly higher levels of Ht (24.0 ± 4, 0 vs 21, 9 ± 4, 9%; p = 0.026). They also had a higher proportion of leg ulcer (31.9% vs 19.6%; p = 0.011) and lower proportion of underweight (38.6% vs 51.8%; p = 0.012), aseptic osteonecrosis (8.5% vs 17.9%; p = 0.013) and subjects receiving hydroxycarbamide (14.9% vs 28.6%; p = 0.007). Table 2 gives the distribution of cardiovascular risk factors in the study population as a whole and according to BP pattern status. Patients with relative hypertension had a significantly higher proportion of smokers (11% vs 0%; p = 0.018), increased PP (13% vs 0%; p = 0.008), low Hb levels (47% vs 39%; p = 0.028), hyperuricemia (57% vs 29%; p = 0.036), microalbuminuria (45 vs 18; p 0.038) and lower proportion of underweight (38% vs 52%; p = 0.012).

Univariate and multivariate factors associated with relative hypertension are summarized in Tables 3. In univariate analysis, leg ulcer, central obesity, smoking, hyperuricemia, microalbuminuria and low Hb levels emerged as the main factors associated with relative hypertension. However, in multivariate analysis, the strength of the associations observed in univariate analysis persisted only for leg ulcer (aOR 2.05; 95%CI 1.77 - 5.18; p = 0.016), central obesity (aOR 3.32; 95%CI 1.28 - 6.24; p = 0.001), smoking (aOR 5.02; 95%CI 1.51 - 9.50; p = 0.017), and microalbumiuria (aOR 3.44; 95%CI 1.44 - 5.76; p = 0.035).

4. Discussion

The main findings of the present cross-sectional study are as follow. First, relative hypertension was a common finding in the preset case series whereas systemic hypertension was rarely seen. Second, leg ulcer, central obesity, smoking and microalbuminuria were the main clinical factors significantly associated with relative hypertension.

Nearly half of steady-state SCD patients had relative hypertension in the present study. Our prevalence is similar to that of 45% reported by Benneh-Akwasi Kuma *et al.* in Ghana [20] as well as of 44% found by Makubi *et al.* [21] and Gordeuk *et al.* [6]. However, it is somewhat higher than that of 17% found by Becker *et al.* [5] and Bodas *et al.* [4], respectively. The observed disparity in relative hypertension prevalence could be explained by differences in methodology, patient's clinical characteristics and thresholds used to define relative hypertension. The mechanisms underlying the relative BP increase in SCD patients are not well understood. However, alterations in blood viscosity may substantially contribute to increase BP [15]. Indeed, hemolysis-induced oxidative stress and subsequent endothelial dysfunction as well as unavailability of nitric oxide (NO) can lead to platelet activation, aggregation and subsequent increase in blood viscosity and peripheral vascular resistance according to Poiseuille law [16]. Relative hypertension has been reported to be associated with an increased risk for renal and pulmonary complications. Indeed, Gordeuck *et al.* [6] reported over a two years follow up trends for more progression to elevated serum

Table 1. Clinical and biological characteristics of the study population as a whole and according to BP pattern status.

Variables	All n = 103	Normal BP n = 56	Relative HT n = 47	p
Gender, n(%)				0.423
M	35(34.0)	20(35.7)	15(31.9)	
F	68(66.0)	36(64.3)	32(68.1)	
Age (years)	26.2 ± 7.9	25.7 ± 8.1	26.8 ± 7.8	0.462
HT family (n, %)	41(39.8)	20(35.7)	21(44.7)	0.234
DS family (n, %)	25(24.3)	14(25)	11(23.4)	0.518
SBP (mmHg)	109.2 ± 13.2	102.2 ± 9.0	127.6 ± 12.6	**<0.001**
DBP (mmHg)	67.6 ± 10.2	60.6 ± 6.2	75.9 ± 7.4	**<0.001**
MAP (mmHg)	81.5 ± 10.1	74.5 ± 6.3	89.8 ± 6.9	**<0.001**
PP (mmHg)	41.7 ± 10.7	41.6 ± 7.6	41.7 ± 13.7	0.935
BMI (Kg/m^2)	18.8 ± 2.6	18.6 ± 2.7	19.0 ± 2.5	0.441
WC, m	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.01	0.236
Transfusion/yr ≥ 3 (n, %)	13(12.6)	7(12.5)	6(12.8)	0.599
VOC/yr ≥3 (n, %)	6(5.8)	3(5.4)	3(6.4)	0.574
HU (n, %)	23(22.3)	16(28.6)	7(14.9)	**0.007**
AON (n, %)	14(13.6)	10(17.9)	4(8.5)	**0.013**
Leg ulcer (n, %)	26(25.2)	11(19.6)	15(31.9)	**0.011**
Priapism (n, %)	6(5.8)	4(7.1)	2(4.3)	0.426
Hb (g/l)	76.0 ± 15.0	74.0 ± 16.0	79.0 ± 13.0	0.053
Ht(%)	22.9 ± 4.6	21.9 ± 4.9	24.0 ± 4.0	**0.026**
Reticulocyte(%)	9.6 ± 3.2	10.0 ± 3.5	9.1 ± 2.4	0.488
BUN (mmol/l)	2.8 ± 0.8	2.8 ± 0.9	2.9 ± 1.0	0.891
Uricacid (µmol/l)	374.9 ± 113	374.9 ± 125.0	381.0 ± 101.2	0.898
Creatinine (µmol/l)	56.6 ± 13.3	60.2 ± 14.2	54.0 ± 11.5	0.508
eGFR, ml/min/1.73 m^2	164.7 ± 36.4	164.3 ± 37.2	165.3 ± 35.8	0.890
ACR (mg/g)	38.3 ± 6.3	33.5 ± 7.7	44.1 ± 6.0	0.320

Data are expressed as mean ± standard deviation, absolute frequency (n) and relative frequency (in percent) Abbreviations: BP, blood pressure HT, hypertension M, male F, female SBP, systolic blood presure DBP, diastolic blood pressure MAP, mean arterial blood pressure PP, pulse pressure BMI, body mass index WC, waist circumference HU, VOC, vaso-occlusive crisis hydroxyurea AON, aseptic osteonecrosis Hb, hemoglobin Ht, hematocrit BUN, blood urea nitrogen eGFR, estimated glomerular filtration rate.

creatinine and tricuspid regurgitant jet velocity (TRV) in SCD patients with relative hypertension in comparison to those with normal BP. They concluded that BP 120 - 139/70 - 89 mmHg defines a category of relative systemic hypertension in SCD patients that is associated with an increased risk of pulmonary artery hypertension and renal dysfunction.

Systemic hypertension was not a common finding in the present case series. Our finding agrees with previous reports of a paradoxical low prevalence of systemic hypertension in SCD in spite of endothelial dysfunction, chronic

Table 2. Cardiovascular risk factors in the study population as a whole and according to BP pattern status.

Variables	All n = 103	Normal BP n = 56	Relative HT n = 47	p
Age, years (n,%)				0.950
18 - 28	71(68.9)	38(67.9)	33(70.2)	
29 - 39	23(22.3)	13(23.2)	10(23.3)	
40 - 50	9(8.7)	5(8.9)	4(8.5)	
Alcohol (n, %)	6(5.8)	3(5.4)	3(6.4)	0.574
Smoking (n, %)	5(4.9)	0(0.0)	5(10.6)	**0.018**
Increased PP (n, %)	6(5.8)	0(0.0)	6(12.8)	**0.008**
BMI < 18.5 Kg/m^2, n(%)	47(45.6)	29(51.8)	18(38.3)	**0.012**
Central obesity, n(%)	8(7.8)	2(3.6)	6(12.8)	**0.005**
Hb < 80 g/l (n, %)	44(42.7)	22(39.3)	22(46.8)	**0.028**
Hyperuricemia (n, %)	43(41.7)	16(28.6)	27(57.4)	**0.036**
RKF, n(%)	4(3.9)	2(3.6)	2(6.4)	0.622
Microalbuminuria (n,%)	31(30.1)	10(17.9)	21(44.7)	**0.038**

Data are expressed as absolute frequency (n) and relative frequency (in percent) Abbreviations: HT, hypertension, BP blood pressure,PP pulse pressure BMI, body mass index Hb, hemoglobin RKF : eGFR < 60 ml/min/1.73 m^2.

Table 3. Univariate and multivariate factors associated with relative hypertension in the study population in logistic regression analysis.

Variable	**Univariate Multivariate**			
	p	OR (95% IC)	p	ORa (95% IC)
Leg ulcer (yes vs no)	0.015	1.92(1.77 - 4.72)	0.016	2.05 (1.77 - 5.18)
Central obesity (yes vs no)	0.006	3.92(1.28 - 5.12)	0.001	3.32 (1.28 - 6.24)
Smoking (yes vs no)	0.015	5.12(1.55 - 7.45)	0.017	5.02 (1.51 - 9.50)
Hyperuricemia (yes vs no)	0.008	3.25(1.57-4.74)	0.796	1.12 (0.47 - 2.67)
Microalbuminuria (yes vs no)	0.013	2.17(1.50 - 2.73)	0.035	3.44 (1.44 - 5.76)
Hb < 80 g/l (yes vs no)	0.003	3.36(1.62 - 4.98)	0.224	1.67 (0.73 - 3.90)
Constant	-	-	0.09	0.281

Variables not entered in the model:PP (pulse pressure).

inflammation and vasculopathy, well-known risk factors for the development and progression of hypertension in the general population [1]. The incidence of hypertension among patients with SCD has been reported to be markedly lower than that of the general population and some patients may have lower than normal BP levels [22]. Potential mechanisms underlying this low prevalence of hypertension in SCD include premature deaths that remove those individuals whose BP might reach hypertensive levels in middle adulthood, higher urinary sodium loss due to hyposthenuria, systemic vasodilatation compensating for

microcirculatory flow disturbances, increased production of prostaglandins, and subsequent reduced vascular reactivity [21] [22]. This observation have important clinical implications that include the possibility that relatively normal BP levels actually represent significant hypertension with the attendant risks of adverse cardiovascular and renal outcomes [22]. In line with the latter observation, some reports have indicated that the prevalence of systemic hypertension in SCD rely upon BP parameters considered to define hypertension and the setting of BP measurement. In this regard, Novelli *et al.* [1] found that pulse pressure, unlike other BP parameters, is associated with markers of hemolytic anemia and cardiovascular risk. Indeed, pulse pressure, SBP, DBP, and MAP were associated with reticulocyte count and hemolytic index. In the present study, patients with relative hypertension in spite of their younger age had in average increased PP levels compared to normotensive ones. Although elevated PP is a marker of arterial stiffness in old people, the association of PP and relative hypertension might be related to increased stroke volume as a compensatory mechanism, similar to that seen in patients with clinical hemolytic anemia [1]. Using ambulatory blood pressure monitoring (ABPM) in SCD patients, Becker *et al.* [5] reported a 35% and 56% prevalence of unrecognized hypertension and non-dipping blood pressure pattern, respectively. They concluded that BP abnormalities in SCD are more common than usually reported. Apart from blood viscosity abnormalities, renal dysfunction could also contribute to the relative increase in blood pressure in SCD patients [23] [24] [25].

Leg ulcer, central obesity, smoking and microalbuminuria were the main factors significantly associated with relative hypertension in the present study. The association of leg ulcer with relative hypertension could be explained by increased viscosity [2] [26] translated in the present study by higher levels of hematocrit in SCD patients with relative hypertension compared to those with normal BP. Indeed, it has been reported that the development of complications in SCD rely upon two phenotypes characterized by either a state of hyperhemolysis or hyperviscosity [15] [27] [28]. The hyperviscosity phenotype with subsequent ischemia confers a high risk of complications such as VOC and aseptic osteonecrosis whereas the hyperhemolysis phenotype with subsequent endothelial dysfunction and chronic inflammation exposes SCD patients to complications such as leg ulcer, priapism, and pulmonary artery hypertension [22] [28]. Central obesity as well as smoking may induce relative increase in BP in SCD patients through direct effect on the kidneys and/or insulin resistance-induced activation of the sympathetic nervous system and renin angiotensin aldosterone system [14] [29] [30]. Microalbuminuria in SCD could be both a cause and a consequence of high blood pressure. Sung *et al.* [31] reported in a prospective longitudinal studies that even with the normal range of urinary albumin excretion (UAE), an increase in urinary albumin to creatinine ratio (UACR) is associated with an increased risk for incident hypertension and cardiovascular mortality. Albuminuria could also be a phenotype of systemic arterial endothelial damage caused by high BP or dysfunction of the endothelium of the glomerular

capillary resulting in altered glomerular filtration function [32]. Indeed, Albuminuria is not only a predictor of development and progression of diabetic and nondiabetic renal diseases, but is a marker of endothelial dysfunction [33].

The interpretation of the results of the present study should take into account of some limitations. First, its cross-sectional design precludes the establishment of temporal associations between variables of interest. Second, the small did not confer much power to statistical tests to identify additional association between variables of interest. Third, clinical and biological parameters were assessed only once with potential risks of under or overestimation of their true values.

5. Conclusion

Relative hypertension was a common finding in the present case series and associated with traditional cardiovascular risk factor as well as factors specific to SCD highlighting the need for measures to prevent its progression towards systemic hypertension and associated cardiovascular and renal disease.

Acknowledgements

We would like to sincerely thank all the staff of hospitals involved in the present study with special thanks to Professor Dr. Leon Tshilolo, Dr. Jéremie Muwonga and Dr. Placide Manzombi. We remain indebted to Dr. Ernest NGONG and Dr. Christelle Ndjali for their commitment as well as to all the participants for their invaluable contribution to the knowledge of sickle cell disease and associated complications.

Author's Contribution

MPI drafted the protocol, collected data, participated in data processing and analysis, drafted the manuscript; LFB revised the protocol and the manuscript, participated in data analysis; MJR revised the protocol and the manuscript, participated in data analysis; NA proceeded to data analysis and revised the manuscript; BJB revised the manuscript; MVM revised the manuscript; LAL revised the manuscript; ZCV revised the manuscript; KFP revised manuscript; NYM revised the manuscript; EYM revised the manuscript; MMM revised the manuscript and participated in data analysis; KEM revised the manuscript; ICK revised the manuscript; EPM revised the manuscript; NMN revised the manuscript.

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