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Influence of Sickle Cell Trait and ABO/RH Blood Groups on the Severity of *Plasmodium sp.* Infection Among Patients from Luanda, Angola

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Influence of Sickle Cell Trait and ABO/RH Blood Groups on the Severity of *Plasmodium sp*. Infection Among Patients from Luanda, Angola

Running title: Sickle Cell Trait and Blood Groups on *Plasmodium sp*. Infection

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Abstract

The African continent carries a high burden of malaria. We evaluated the influence of sickle cell traits and blood groups (ABO/Rh) with the clinical conditions and outcome of *Plasmodium sp*. infection in patients admitted in Josina Machel Hospitals, Luanda, Angola. This was a cross-sectional study conducted with 102 malaria inpatients during the second semester of 2023. Patients with AA haemoglobin comprised 36.3%, followed by AS (39.2%) and SS (24.5%). About 12% of SS patients presented high parasitemia. Moreover, 20% and 16% of SS patients presented severe disease and death, respectively. The ORh+ individuals were the majority (40.2%). About 37% presented high parasitemia, 44% presented low haemoglobin levels, 17% presented severe disease, and 15% had an unfavourable clinical outcome. Our results showed a high rate of disease severity and mortality among patients with malaria in the SS or ORh+ group.

Keywords: blood groups; sickle cell trait; malaria; severity

Introduction

The latest World Malaria Report from the WHO indicates that in 2022, nearly half of the global population was at risk of contracting malaria. Approximately 250 million cases were reported worldwide, resulting in an estimated 608,000 deaths. The African continent carries a disproportionately high burden of malaria, with Angola being one of the most affected countries in the region. Malaria remains endemic in Angola and is consistently the leading cause of death almost every year [1,2].

The ABO blood group system is the most important blood grouping system in clinical practice. It has several roles, including acting as receptors for bacteria, parasites, foreign substances, and viruses and serving as transporters, channels, structural proteins, adhesion molecules, and enzymes. Blood group O is more common among populations, especially in regions where malaria is prevalent [3,4]. Sickle cell anaemia is the most common monogenic disease globally and, similar to malaria, is more prevalent in sub-Saharan African countries. This disorder is characterised by haemoglobin S

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(HbS). This mutation arises from a hereditary structural change due to substituting one amino acid in the normal globin chain [5]. Similarly, the emergence of the HbS mutation is associated with selective protection (natural selection) against the most lethal forms of malaria. This enhances the fitness of heterozygous individuals (HbAS) in the context of malaria, compensating for the potential loss of homozygotes (HbSS), in whom malarial infection is often fatal [6].

Our research team in Angola has conducted several studies to evaluate the impact of blood groups on different diseases, such as SARS-CoV-2 infection[8], HIV infection[9], leprosy [10], chronic kidney disease, hypertension, and other non-communicable chronic diseases [11,12], nephrotic syndrome (NS) and sickle cell anemia [13], uremic conditions [14], arterial hypertension [15], diabetes [20], changes in hemograms in malaria [18], among others [16,17]. However, we continue to question the relationship between blood groups and sickle cell traits. Herein, we evaluated the influence of sickle cell traits and blood groups (ABO/Rh) with the clinical conditions and outcome of Plasmodium sp. infection in patients admitted in Josina Machel Hospitals in Luanda, the capital city of Angola.

Methodology

Study Design and Settings

This was a cross-sectional study conducted to understand the association between sickle cell trait and blood groups (ABO/Rh) with the severity of *Plasmodium* sp. infection in patients hospitalized in tertiary-level hospitals in Luanda, during the second semester of 2023. A total of 200 patients were invited and freely consented to participate in the study. Those unable to provide blood samples or informed consent were excluded from the study population. Among the 200 patients found, only a sample of 102 patients met the inclusion criteria. Patients aged 12 to 66 years hospitalised for malaria were included. Patients with a history of hypertensive disease, diabetes, chronic kidney disease, cerebral malaria, low immunity, and other chronic diseases that may contribute to increasing the chances of error in data analysis were excluded. The study protocol was reviewed and approved by the Scientific Board of the Health Sciences Institute, Agostinho Neto University (118/GD/ICISA/UAN/2021), and the Clinical Management of Josina Machel Hospital (36/DPC/HJM/2023).

Data/Sample Collection and Laboratory Procedure

Blood samples were collected via venous puncture for a rapid malaria test (SD-Bioline Malaria AG Pf). Rapid tests for detecting *P. falciparum* and *P. vivax*, as well as microscopic evaluations, confirmed the exclusive presence of *P. falciparum*. Whole blood samples were collected via capillary puncture into EDTA tubes and thick blood smears. After collection, samples were sent to the National Health Research Institute (INIS) for laboratory processing. The microscopic technique (Evident Olympus, Tokyo, Japan) with Giemsa-stained thick smears was used to confirm rapid test results by direct visualisation of the parasite. Patients with parasitemia ≤1,000 parasites per cubic millimetre (p/mm^3) were classified as low or moderate parasitemia, while those with parasitemia >1,000 p/mm^3 were classified as high parasitemia [15]. Haemoglobin electrophoresis was performed using the GíantHS - Cell cellulose acetate electrophoresis system (CELL-Start Project, Cologno Monzese, Italy) [13]. ABO and Rh blood typing was carried out using the microplate technique [19–21]. The haematological analyser MINDRAY BC-780 (Mindray, Shenzhen, China) was employed for complete blood counts, from which only haemoglobin (Hb) and hematocrit (Hct) values were extracted [17,18].

Statistical Analysis

Descriptive analyses, including absolute and relative frequencies, were conducted to summarise the data, including the calculation of means for quantitative variables. All statistical procedures were carried out using SPSS version 25.

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Results

Distribution of ABO/Rh blood groups and hemoglobin types are presented in Table 1. Patients with AA haemoglobin comprised 36.3% (37/102) of the studied population, followed by AS (39.2%, 40/102) and SS (24.5%, 25/102). The ORh+ individuals were the majority (40.2%, 41/102), with SS accounting for 56% (14/25), AA for 35.1% (13/37), and AS for 35.0% (14/40). ARh+ individuals represented 24.5% (25/102), among whom 27.0% (10/37) were AA and 30% (12/40) were AS. The highest mean parasitemia (4,618.00 parasites/mm^3) was observed in ARh+ patients.

Table 1. Blood groups and haemoglobin types.

	Types of Haemoglobins				Mean
	AA=37	AS=40	SS=25	Total	Pf(mm3)
Blood Group	(36.3%)	(39.2%)	(24.5%)	(n=102)	2445.59
ABRh+	3 (8.1)	5 (12.5)	0 (0.0)	8 (7.8)	656.25
ARh-	3 (8.1)	0 (0.0)	0 (0.0)	3 (2.9)	50
ARh+	10 (27.0)	12 (30.0)	3 (12.0)	25 (24.5)	4618
BRh+	8 (21.6)	8 (20.0)	5 (20.0)	21 (20.6)	2130.95
ORh-	0 (0.0)	1(2.5)	3 (12.0)	4 (3.9)	1025
ORh+	13 (35.1)	14 (35.0)	14 (56.0)	41 (40.2)	1945.12

The study participants were predominantly young, with around 83% being under 40 years of age (Table 2). The age group between 21 and 40 years was predominant (55.9%, 57/102), followed by individuals aged 14 to 20 years (27.7%, 28/102). The SS individuals were mostly patients aged 21 to 40 years (52%, 13/25), where ORh+ patients represented 46.3% (n=19/40) and those aged 14 to 20 years (28.5%), where ORh+ patients represented 34.1% (n=14/40). The highest mean parasitemia was observed in individuals aged 21 to 40 years (3485.96 p/mm^3). The majority of individuals from other blood groups were aged between 20 to 40 years, accounting for 62.3% (38/61) of the non-ORh+ individuals. Regarding gender, it was found that 60.8% (62/102) of the participants were female, and it was also among women that the majority of SS individuals (60%, 15/25), ORh+ individuals (61.0%, 25/41), and non-ORh+ individuals (60.7%, 37/61) were observed. However, individuals without sickle cell trait were predominantly observed in men (22/102, 59.5%). The highest mean parasitemia was observed in male individuals (4812.96 p/mm^3), which was 5 times more than observed in females.

Table 2. Sickle cell trait, blood groups, age ranges, and gender.

Independent variables	Types of Haemoglobins			Total (n=102)	Blood groups		Mean *Pf(mm3)* 2445.59
	AA =37 (36.3 %)	AS =40 (39.2%)	SS =25 (24.5%)		ORh+=40 (40.2%)	Others =61 (59.8%)	
Age group							
14-20				28		14	
	13(35.1)	8(20.0)	7(28.0)	(27.5)	14 (34.1)	(22,9)	1080.36
21-40				57		38	
	19(51.4)	25(62.5)	13(52.0)	(55.9)	19 (46.3)	(62.3)	3485.96
41-60	3(8.1)	4 (10)	2 (8.0)	9 (8.8)	4 (9.8)	5 (8.2)	1905.56
>61	2(5.4)	3 (7.5)	3 (12.0)	8 (7.8)	4 (9.8)	4 (6.6)	418.75
Gender							

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Female				62		37	
	15(40.5)	32(80.0)	15(60.0)	(60.8)	25 (61.0)	(60.7)	918.55
Male				40		24	
	22(59.5)	8 (20.0)	10(40.0)	(39.2)	16 (39.0)	(39.3)	4812.50

In Table 3, it was observed that the most commonly reported symptom was fever, affecting 62.7% (64/102) of the patients, followed by headache (59.8%, 60/120). Among SS patients, fever and headache accounted for 56% and 44%, respectively, followed by weakness (56%), body aches (40%), and vomiting (36%). Among AA individuals, chills (73%), fever (67%), and weakness (56%) were the most reported symptoms. Among AS individuals, fever (62.5%), headache (55%), and weakness (37%) were the most commonly mentioned complaints.

Table 3. Sickle cell trait, blood groups, and symptoms.

	Types of haemoglobin				**blood groups**		
Clinical symptoms	**AA =37 (36,3%)**	**AS =40 (39,2%)**	**SS =25 (24,5%)**	**Total (n=102)**	**ORh+ (41, 40,2%)**	**Others (61, 59,8%)**	**Average *Pf(mm³)* 2445,59**
Headache	27(73,0)	22(55,0)	11(44,0)	60 (58,8)	22(53,7)	38(62,3)	3560,83
Fever	25 (67,6)	25 (62,5)	14(56,0)	64 (62,7)	25 (61,0)	39 (63,9)	3005,47
Chills	0 (0,0)	4(10,0)	1(4,0)	5 (4,9)	2(4,9)	3 (4,9)	830,00
Weakness	21 (56,8)	15 (37,5)	14(56,0)	50 (49,0)	26 (63,4)	24 (39,3)	3940,00
Body aches	11 (29,7)	11(27,5)	10(40,0)	32 (31,4)	11(26,8)	21 (34,4)	1154,69
Vomiting	10 (27,0)	6(15,0)	9 (36,0)	25 (24,5)	10(24,4)	15 (24,6)	986,00
Abdominal pain	8 (21,6)	5 (12,5)	5 (20)	18 (17,6)	8 (19,5)	10 (16,4)	1527,78
Coma	0 (0,0)	1(2,5)	0 (0,0)	1 (1,0)	0 (0,0)	1(1,6)	50,00
Hallucinations	1(2,7)	1(2,5)	1(4,0)	3 (2,9)	1(2,4)	2(3,3)	1666,67
Seizures	3 (8,1)	0(0,0)	5(20,0)	8 (7,8)	4(9,8)	4 (6,6)	893,75
Others	6 (16,2)	9 (22,5)	2 (8,0)	17 (16,7)	7 (17,1)	10 (16,4)	626,47

Among individuals in the Rh+ group, weakness (63%), fever (61%), and headache (53%) were the most common complaints, while among individuals from other blood groups, fever (63%), headache (62%), weakness (39%), and body aches (34%) were the most frequently reported symptoms. Patients with weakness (3940.00 p/mm^3), headache (3560.83 p/mm^3), and fever (3005.47 p/mm^3) had the highest mean parasite counts.

Table 4. Sickle cell trait, blood groups, and antimalarial drugs.

	Types of Haemoglobins				**Blood groups**		
Antimalarial drugs	**AA (n=37)**	**AS (n=40)**	**SS (n=25)**	**Total (n=102)**	**ORh+ (n=41)**	**Others (n=61)**	**Mean**

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							Pf (p/mm³)
Artesunate	23 (62.2%)	20 (50.0%)	12 (48.0%)	55 (53.9%)	24 (58.5%)	31 (50.8%)	3323.64
Artemether	7 (18.9%)	9 (22.5%)	6 (14.6%)	18 (17.6%)	6 (14.6%)	12 (19.7%)	2083.33
Coartem	6 (16.2%)	11 (27.5%)	9 (36.0%)	26 (25.5%)	10 (24.4%)	16 (26.2%)	1115.38
Paracetamol	13 (35.1%)	10 (25.0%)	13 (52.0%)	36 (35.3%)	10 (24.4%)	26 (42.6%)	3788.89
Dipyrone	15 (40.5%)	17 (42.5%)	7 (28.0%)	39 (38.2%)	19 (46.3%)	20 (32.8%)	1650
Omeprazole	8 (21.6%)	17 (42.5%)	5 (20.0%)	30 (29.4%)	16 (39.0%)	14 (23.0%)	775
Ciprofloxacin	7 (18.9%)	2 (5.0%)	4 (16.0%)	13 (12.7%)	4 (9.8%)	9 (14.8%)	1807.69
Amoxicillin	4 (10.8%)	1 (2.5%)	8 (32.0%)	13 (12.7%)	4 (9.8%)	9 (14.8%)	350
Ceftriaxone	6 (16.2%)	8 (20.0%)	3 (12.0%)	17 (16.7%)	8 (19.5%)	9 (14.8%)	1797.06
Metronidazole	5 (13.5%)	3 (7.5%)	1 (4.0%)	9 (8.8%)	6 (14.6%)	3 (4.9%)	1911.11
Vitamin B Complex	5 (13.5%)	11 (27.5%)	6 (24.0%)	22 (21.6%)	9 (22.0%)	13 (21.3%)	2202.27
Folic Acid	4 (10.8%)	5 (12.5%)	7 (28.0%)	16 (15.7%)	8 (19.5%)	8 (13.1%)	1490.62
Diazepam	3 (8.1%)	0 (0.0%)	3 (12.0%)	6 (5.9%)	2 (4.9%)	4 (6.6%)	4533.33
Saline Solution	28 (75.7%)	22 (55.0%)	7 (28.0%)	57 (55.9%)	22 (53.7%)	35 (57.4%)	3315.79
Others	10 (27.0%)	9 (22.5%)	9 (36.0%)	28 (27.5%)	12 (29.3%)	16 (26.3%)	675

The most prescribed antimalarial drugs among patients were Artesunate (53.9%, 55/102), followed by Coartem (25.5%, 26/102) and Artemether (17.6%, 18/102). SS patients were mostly treated with Artesunate (48%) and Coartem (25%), while medications such as paracetamol (52%) and Amoxicillin (32%) were also widely used in these patients. AA individuals were mainly treated with Artesunate (62%); however, Dipyrone (40%) and saline solution (75%) were also frequently administered to these patients. Individuals were treated with Artesunate (50%), Dipyrone (42%), Omeprazole (40%), and saline solution (55%).

In individuals from the ORh+ group, Artesunate was administered to 58% (24/40) of patients, and Omeprazole (39%), Dipyrone (46%), and saline solution (53%) were also widely used in ORh+ patients. Patients from other blood groups also received Artesunate (50%) as the antimalarial, and other drugs like paracetamol (42%) and saline solution (57%) were frequently used in the treatment of these patients. Individuals treated with Diazepam (4533.33 p/mm³), Paracetamol (3788.89 p/mm³),

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saline solution (3315.79 p/mm^3), and Artesunate (3323.64 p/mm^3) showed a higher degree of parasitemia.

In Table 5, it was found that the majority of patients presented with low parasitemia (≤50 p/mm^3) at admission, representing approximately 54.9% (56/102) of the studied patients. SS patients predominantly presented with low parasitemia (80%), while high parasitemia was mainly observed in AA (35%) and AS (25%) individuals. ORh+ patients predominantly presented with high parasitemia (36.6%).

Table 5. Sickle cell trait, blood groups, parasitemia, haemoglobin, and hematocrit levels.

Laboratory index	Hemoglobin Types			Total (n=102)	Blood Groups		Mean Pf(mm^3)
	AA 37 (36.3%)	AS 40 (39.2%)	SS 25 (24.5%)		ORh+ (%) 41 (40.2%)	Others 61 (59.8%)	
Parasitemia							
< 51 (low)	17 (46.0%)	19 (47.5%)	20 (80.0%)	56 (54.9%)	14 (34.1%)	42 (68.9%)	50.00
51-1000 (moderate)	7 (18.9%)	11 (27.5%)	2 (8.0%)	20 (19.6%)	12 (29.3%)	8 (13.1%)	882.50
> 1000 (high)	13 (35.1%)	10 (25.0%)	3 (12.0%)	26 (25.5%)	15 (36.6%)	11 (18.0%)	8807.69
Haemoglobin (mg/dL)							
< 10 (low)	19 (51.4%)	14 (35.0%)	13 (52.0%)	46 (45.1%)	18 (43.9%)	28 (45.9%)	1309.78
10-17 (normal)	17 (46.0%)	26 (65.0%)	12 (48.0%)	55 (53.9%)	22 (53.7%)	33 (54.1%)	3421.82
> 17 (high)	1 (2.7%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (2.4%)	0 (0.0%)	1000.00
Hematocrit (mg/dL)							
< 31.4	23 (62.2%)	21 (52.5%)	18 (72.0%)	62 (60.8%)	24 (58.5%)	38 (62.3%)	1391.13
31.5-50	13 (35.1%)	18 (45.0%)	6 (24.0%)	37 (36.3%)	15 (36.6%)	22 (36.1%)	4328.38
> 50	1 (2.7%)	1 (2.5%)	1 (4.0%)	3 (2.9%)	2 (4.9%)	1 (1.6%)	1016.67

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Regarding haemoglobin levels, as expected, SS individuals showed low haemoglobin (≤9 mg/dL). Surprisingly, the majority of AA individuals (51%) also presented with low haemoglobin. Among ORh+ patients, most exhibited normal haemoglobin levels (54%) and low haemoglobin (43%), whereas in patients from other groups, individuals with normal haemoglobin accounted for 54% and low haemoglobin for 45%.

In the assessment of hematocrit levels, it was found that 72% of individuals had hematocrit values below the reference range (≤31.4 mg/dL). The same phenomenon was observed in AA (62%) and AS (52%) individuals. Among non-ORh+ individuals, 62% presented hematocrit values below the reference range, while for ORh+ individuals, the percentage was 58%. However, the highest degree of parasitemia was observed in individuals with normal hematocrit levels.

In Table 6, it was observed that the majority of patients presented with mild (40%, 41/102) and moderate (44%, 45/102) clinical conditions, with only 15.7% (16/102) classified as severe. It was noted that 20% of SS patients were severe, 24.3% of AA patients presented the same condition, and only 5% of AS patients were severe. Among individuals in the ORh+ group, severe cases represented 17%, while in non-ORh+ individuals, the percentage was 14.8%. Severe patients showed a higher mean parasitemia level (7643.85 p/mm^3).

Table 6. Sickle cell trait, blood groups, and symptoms.

Clinical Condition	Hemoglobin Types			Total	Blood Groups		Mean
	AA =37 (36,3%)	AS =40 (39,2%)	SS =25 (24,5%)	(n=102)	ORh+=41 (40,2%)	Others=61 (59,8%)	Pf(mm^3) 2445.59
Severity							
Mild	11 (29.7%)	25 (62.5%)	5 (20.0%)	41 (40.2%)	13 (31.7%)	28 (45.9%)	1364.63
Moderate	17 (46.0%)	13 (32.5%)	15 (40.0%)	45 (44.1%)	21 (51.2%)	24 (39.3%)	1582.22
Severe	9 (24.3%)	2 (5.0%)	5 (20.0%)	16 (15.7%)	7 (17.1%)	9 (14.8%)	7643.85
Outcome							
Discharge	32 (86.5%)	36 (90.0%)	16 (64.0%)	84 (82.4%)	32 (78.1%)	52 (85.2%)	2517.26
Transfer	2 (5.4%)	2 (5.0%)	5 (20.0%)	9 (8.8%)	3 (7.3%)	6 (9.8%)	3427.78
Death	3 (8.1%)	2 (5.0%)	4 (16.0%)	9 (8.8%)	6 (14.6%)	3 (4.9%)	794.44

Regarding clinical outcomes, 82% (84/102) of patients were discharged. The malaria mortality rate was higher in SS individuals (16%), followed by AA (8%) and AS (5%). The highest level of parasitemia was observed in individuals who were discharged (3427.78 p/mm^3).

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Discussion

Investigating demographic, clinical, and genetic conditions is essential for a better understanding of the clinical profile, severity, and mortality associated with malaria, particularly in high-endemic regions such as Angola. This study contributes valuable insights into the impact of sickle cell trait and ABO/Rh blood groups on the clinical course and outcomes of Plasmodium sp. infection among patients in Luanda, the capital city of Angola.

In agreement with our findings, a study conducted in Ethiopia reported a mean age of 24.67 ± 11.2 years among malaria patients, with the majority aged between 16 and 30 years and presenting moderate parasitemia levels — a demographic profile similar to that of our study population [25]. Regarding blood groups, a study in Ghana found that 45.1% of malaria patients belonged to blood group O, with approximately 35.7% being ORh+ [23], a distribution pattern also observed in our population.

Concerning haemoglobin variants, a study from Cameroon showed a higher prevalence of P. falciparum gametocyte carriage among individuals with HbAS (18.47%) compared to those with HbAA (13.57%) [22]. In contrast, our analysis revealed lower parasitemia levels in sickle cell anaemia (SS) patients (12%) compared to heterozygous (AS, 25%) and normal (AA, 35%) individuals [24]. This finding may reflect a possible immunological adaptation in SS individuals, despite their greater clinical severity and adverse outcomes.

A study in Indonesia identified 17 common symptoms of malaria, with fever being the most frequent yet non-specific indicator. Therefore, severe symptoms such as jaundice, anaemia, loss of consciousness, dark urine, and splenomegaly were considered more indicative of advanced malaria [26]. In our cohort, symptoms such as fever, headache, weakness, and vomiting were more frequently reported by SS and ORh(+) patients, who also showed higher rates of severe malaria.

Regarding treatment, we observed that, in addition to antimalarial drugs, various other medications were administered, consistent with findings from a previous study by our group. Most patients received Artemether (90.9%), saline solution (52.3%), dipyrone (64.1%), and other supportive drugs such as metoclopramide, B complex vitamins, ciprofloxacin, and diazepam [19], reflecting the multifactorial clinical approach used in local practice.

Although this study assessed only hemoglobin and hematocrit, previous work by our group showed that AA individuals with ARh(−) blood type had the lowest mean hemoglobin levels (6.95 ± 1.7 g/dL), compared to SS patients from A (8.6 ± 2.2), B (7.4 ± 2.2), and O (9.9 ± 4.4) groups, all Rh(+). ARh(−) patients also presented the lowest average erythrocyte count, MCV, and MCH, whereas MCHC values were elevated in all profiles [18].

In the current study, the highest rates of disease severity, mortality, and hospital transfer were observed among SS patients, highlighting their increased vulnerability to malaria infection. While our previous study indicated a high rate of severe malaria in ABRh(+) individuals [18], current findings show greater clinical impact among ORh(+) and SS patients.

This study presents some limitations. The cross-sectional design limits the ability to establish causality between sickle cell trait, blood group, and malaria severity. The sample size was relatively small (n = 102), which may reduce the statistical power and generalizability of the findings. Additionally, the exclusion of patients with chronic comorbidities and cerebral malaria may have underestimated the overall disease severity. Only haemoglobin and hematocrit levels were analysed, limiting the scope of haematological insights. Finally, the study was conducted in a single city and during a specific period, restricting broader geographic or seasonal conclusions. Despite this, the study evaluates the combined influence of genetic factors such as sickle cell trait and ABO/Rh blood groups on the severity of Plasmodium falciparum infection, an approach that can be further explored in future studies in Angola.

Conclusion

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Our findings showed that genetic factors such as sickle cell trait (AS or SS) and ABO/Rh blood groups influence malaria severity in Luanda, Angola. In our study, SS and ORh+ individuals had high rates of disease severity and mortality, highlighting the importance of genetic screening for malaria control in endemic regions of sub-Saharan Africa.

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Data Availability Statement: All data is available upon reasonable request to the corresponding author.

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Conflict of Interest Statement: The authors declare no conflicts of interest.

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