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Can *Plasmodium falciparum* Induce Homocysteinemia in Malaria Patients?

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Abstract

Background: *Plasmodium falciparum* has developed elaborate strategies to survive in the hostile intracellular environment of the infected host cell, including resistance to oxidative stress. Cysteine is a metabolic product of homocysteine and a precursor of the antioxidant glutathione used by *Plasmodium falciparum* to escape harmful oxidation. **Objectives**: In the present study we aimed to assess whether *Plasmodium falciparum* can induce homocysteinemia in malaria patients of Burkina Faso. **Methods**: Eighty-five (85) individuals including 25 affected by severe malaria, 44 by simple malaria, and 12 negative controls for *P. falciparum* infection were included in the present study. An enzymatic assay of plasma homocysteinemia was performed using the Homocysteine Enzymatic Assay reagent (ref 05385415 190) on the Roche/Hitachi Cobas c. **Results**: The results of the present study show that the mean plasma homocysteine concentrations were 15.1 ± 8.4 µmol/L among patients with severe malaria, 14.0 ± 6.0 µmol/L in patients with uncomplicated malaria, and 12.6 ± 4.1 µmol/L in negative controls for malaria parasite. **Conclusions**: Our findings suggest high homocysteinemia in malaria patients, especially in those with severe malaria. Monitoring homocysteinemia in the latter group will be useful to avoid complications when an elevated plasma level of homocysteine is a known risk factor for cardiovascular diseases.

Keywords

Homocysteine, Malaria, Burkina Faso

1. Introduction

The essential amino acid, methionine, is the only source of homocysteine (Hcy) in humans and is found in dietary protein [1]. Hcy, a sulfur-containing non-protein amino acid is an essential intermediate in the normal mammalian metabolism of methionine. Hcy levels are maintained dynamically by either a remethylation into methionine or transsulfuration into cysteine (**Figure 1**). Part of homocysteine is remethylated in the liver by the action of betaine-Hcy methyltransferase using methyltetrahydrofolate and betaine as methyl donors, respectively. Thus, both CBS, MS and MTHFR enzyme activity as well as the availability of THF (tetrahydrofolates) from folic acid metabolism play an important role in cell Hcy balance

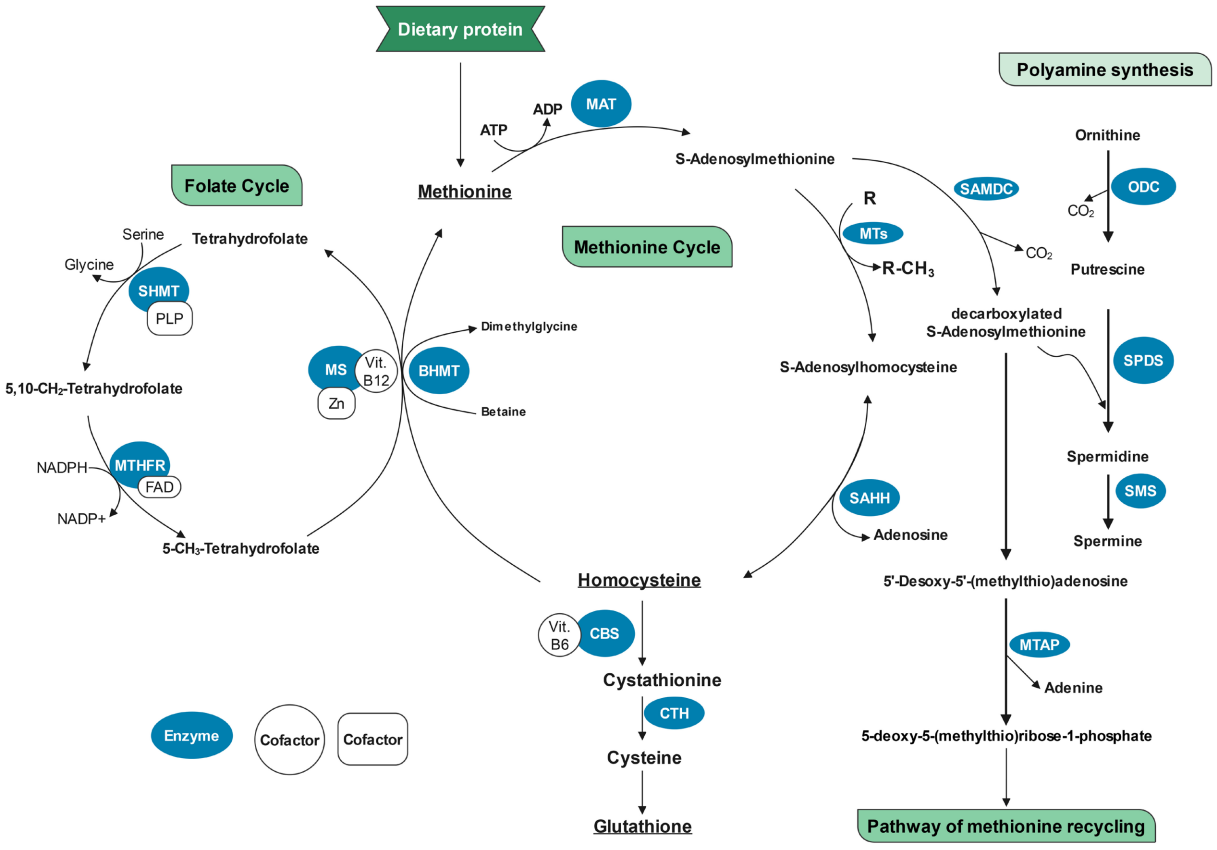

Figure 1. Methionine-homocysteine cycle and polyamines pathways. Legend: BHMT = betaine-homocysteine S-methyltransferase; CBS = cystathionine-β-synthase; CTH = cystathionine-gamma-lyase; FAD = flavin adenine dinucleotide; MAT = methionine adenosyltransferase; MS = methionine synthase; MTAP = S-methyl-5'-thioadenosine phosphorylase; MTHFR = 5,10-methylenetetrahydrofolate reductase; MTs = methyl transferases; ODC = ornithine decarboxylase; PLP = pyridoxal 5'-phosphate; SAHH = S-adenosyl-L-homocysteine hydrolase; SHMT = serine hydroxy-methyltransferase; SMDC = S-adenosylmethionine decarboxylase; SMS = spermine synthase, SPDS = spermidine synthase; Vit. B12 = Vitamin B12 (Cobalamin); Vit. B6 = vitamin B6 (pyridoxine).

[2]. Normal values of plasmatic levels of Hcy have been described as around 5 - 15 μmol/L when higher levels of Hcy are put into three main categories: mild (15 to 30 μmol/L), moderate (30 to 100 μmol/L), and severe, greater than 100 μmol/L [3]. An elevated blood level of homocysteine is an independent risk factor for cardiovascular disease [4], neuropsychiatric pathologies such as Alzheimer's disease [5], neural tube closure defect [6] [7], depressive disorders [8] and schizophrenia [9] [10] [11]. Hyper-homocysteinemia could be due to the inhibition of the remethylation pathway or saturation of the transsulfuration pathway with alteration of coordinate regulation of homocysteine metabolism by S-adenosylmethionine. Moderate hyperhomocysteinemia is prevalent in developed countries due to increasing food intake of animal proteins, a source of methionine and homocysteine and also the processing and preservation of foodstuffs, susceptible to induce a lack of folic acid, vitamins B6 and B12, required for homocysteine metabolism [12].

Studies reported that hyperhomocysteinemia is more common in the Caucasian population with more than 15% of people affected by an elevated blood homocysteinemia [13] while the plasma concentration of Hcy is lower in the sub-Saharan African populations than in the Mediterranean populations [13] [14].

Such a difference is thought to be due to the variable frequency of MTHFR polymorphism in these populations [15]. In Burkina Faso, a study reported a low blood level of homocysteinemia in the general population [13]. The transsulfuration pathway is a metabolic pathway where the transfer of sulfur from homocysteine to cysteine occurs and promotes the generation of glutathione (GSH) (**Figure 1**). The complexity of the Hcy and methionine metabolic pathways and the balance required for hemostasis is strongly influenced by the presence of *Plasmodium falciparum* [16]. Due to the drastic changes observed in the metabolism of GSH in red blood cells infected with *P. falciparum*, de novo synthesis of the tripeptide was found to be required for the parasite survival [17]. *P. falciparum* employs a complex thioredoxin and glutathione system to maintain the intracellular redox balance [18]. The redox system plays an important role in the survival of *P. falciparum* and the progression of the associated disease [19]. Red blood cells can further expel homocysteine accumulated in plasma where it is known to concentrate during malaria infection. These observations are in line with the fact that malaria patients have elevated levels of plasma homocysteine [20]. *Plasmodium falciparum* uses the polyamine pathway (**Figure 1**), which is essential for its proliferation and differentiation, imposing oxidative stress on the host cell [21], following the use of glutathione [22]. This reduces the remethylation of homocysteine to methionine and increases the pathway of transsulfuration.

The folate pathway is an important carbon source for *P. falciparum* in the nucleic acid synthesis. One of the most important carbon transfer reactions in malaria parasites is the methylation of the nucleotide deoxyuridine 5'-monophosphate to deoxythymidine 5'-monophosphate, a precursor to deoxythymidine 5'-triphosphate required for the synthesis of DNA, in the thymidylate cycle [23].

The parasite is also able to oxidize vitamin B12 and thus inhibit the activation of methionine synthase required for remethylation of homocysteine into methionine, leading to increase plasma level of homocysteine in infected patients [16].

Mobilization of glutathione by the malaria parasite to resist oxidative stress promotes the accumulation of homocysteine in the host cell. Previous studies reported an association between human genetic factors and the progression to severe malaria with an increasing level of plasma Hcy [24] [25].

A methionine-rich diet could influence plasma levels of Hcy in the general population. Deep knowledge of homocysteinemia in the Burkinabe population is important to reduce morbidity and mortality due to malaria. Homocysteinemia is generally increased in renal pathology and some authors recommend that research on total homocysteinemia in the general population should include markers of renal function [26]. According to WHO criteria, malaria is considered severe when one or more vital functions of the body (kidneys, liver, etc.) are affected by the disease. In line with such recommendation, we perform some biochemical parameters along with the measurement of homocysteinemia in the present study which aimed to assess whether *Plasmodium falciparum* can induce homocysteinemia in malaria patients of Burkina Faso.

2. Materials and Methods

2.1. Setting and Type of Study

This cross-sectional study was carried out from September to December 2020 in Ouagadougou, the capital of Burkina Faso, with approximately 2,966,307 inhabitants [27]. Ouagadougou is located in the plateau central region with a Sudano-Sahelian climate and two seasons. The dry season is from October to May and the wet season is from June to September. This climate is characterized by the seasonal transmission of malaria mainly during the wet season. However, the presence of peripheral artificial water reservoirs (dam) and residual (open gutters) through the city and the galloping urbanization, leads to a permanent transmission of malaria throughout the year.

2.2. Study Population

The study population consisted of eighty-five (85) patients seen in general medicine at three health facilities in Ouagadougou, CHU de Bogodogo, CMA de Kossodo and Clinique ILBOUDO Bruno. Patients with suspected malaria and referred to the laboratory for a thick smear for malaria diagnosis were included in the study.

2.3. Sampling

A sample of 8 mL of venous blood was collected in three different tubes (EDTA, Sec and/or heparinized) and used for Blood Formula Count (CBC) and thick drop. EDTA tubes were centrifuged at 3000 rpm for 5 mins and aliquots of pellet and plasma were carried out in cryotubes and stored at −80˚C for the homo-

cysteine assay. The blood in the dry or heparinized tubes was separated into pellet and plasma or serum for further biochemical testing.

2.4. Biological Analysis

The thick drop was performed according to the standard method and stained with Giemsa diluted 1/10 [27].

The various hematological parameters were analyzed using the SYSMEX XN-350 device. The enzymatic assay of plasma homocysteine was carried out with the Homocysteine Enzymatic Assay reagent (ref 05385415 190) on the Cobas 6000 C501, E601 device. The assay of transaminases (ASAT: aspartate aminotransferases and ALAT: alanine aminotransferases), serum creatinine and C-reactive protein (CRP) was carried out using the same Cobas device.

2.5. Statistical Analysis

Data were processed using Excel 2019 software (Microsoft) and SPSS® software version 20 (SPSS Inc., Chicago, USA). Pearson's Chi-square test was used for the comparisons and any P value < 0.05 was considered statistically significant.

2.6. Ethical Consideration

The study received the approval of the Burkina Faso health research ethics committee (deliberation N˚ 2020-10-232) as well as that of the internal ethics committee of CHU-B. All participants or legal guardians of those under the age of 18 gave their free and informed consent to participate in the present study.

3. Results

3.1. Sociodemographic Data

The present study population consisted of 40% (34/85) of men (**Figure 2**). The mean age was 20.7 ± 22.2 years. The most represented age group (34.13%) was children (29/85) under 5 years old (**Figure 2**).

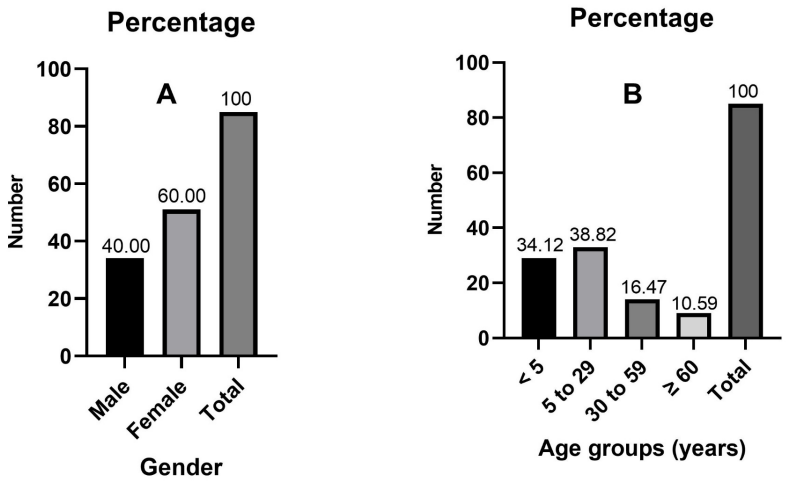

Figure 2. Sociodemographic data of the study population. (A) Gender, (B) age groups.

3.2. Thick Smear Assay and Hematological Parameters

The thick smear assay revealed 73 cases of malaria including 25 severe malaria and 48 uncomplicate malaria against 12 malaria negative individuals (Table 1). The mean age of women was 23.9 ± 22.7 years compared to 15.9 ± 20.8 years for men in the study population. The mean age was 13.1 ± 12.2 years for patients with severe malaria versus 44.5 ± 29.6 years for malaria negative subjects. An average parasite density of 120827.6 ± 244,587 trophozoites/µl was observed in patients with severe malaria compared to 2393.8 ± 2748.4 trophozoites/µl in patients with uncomplicated malaria. A mean hemoglobin level of 6.7 ± 4.0 g/dl was found in patients with severe malaria versus 9.8 ± 3.3 g/dl in malaria negative controls. The mean platelet count in the study population was greater than 150,000 platelets/µl of blood (Table 1).

3.3. Biochemical Parameters

The mean level of transaminases was less than 35 IU/µl (Table 2) while that of CRP was above the reference value (<6 mg/L) (Table 2). Elevated mean serum creatinine was observed in females (192.7 µmol/L) as well as in malaria negative controls (218.9 µmol/L). The mean plasma homocysteinemia level was 14.1 ± 5.4 µmol/L in men and 14.2 ± 7.3 µmol/L in women. In patients with severe malaria the mean plasma homocysteinemia was 15.1 ± 8.4 µmol/L versus 14.0 ± 6.0 µmol/L in individuals with moderate malaria and 12.6 ± 4.1 µmol/L in individuals not infected with *Plasmodium falciparum* (Table 2).

Table 1. Thick smear results, gender, malaria classification and hematological parameters.

		Age	Parasite density (trophozoïtes/µL)$^{\alpha}$	Hb Level (g/dl)$^{\beta}$	Leukocytes (Number/µl)$^{¢}$	Rate of platelets (Number/µl)§	Hcy (µmol/L)$^{\alpha\beta¢\S}$
Sex	Male	15.9 (±20.8)	13622.9 (±32606.4)	9.3 (±2.3)	11097.6 (±8658.2)	151500.0 (±813.8%)	14.1 (±5.4)
	Female	23.9 (±22.7)	52400.2 (±179996.5)	9.3 (±2.9229)	8762.3 (±4139.4)	195100.0 (±113328.3)	14.2 (±7.3)
Thick smear results	Positive	16.7 (±18.2)	42953.3 (±152145.9)	9.3 (±3.5)	9597.7 (±5934.5)	174415.1 (±104592.7)	14.4 (±6.9)
	Negative	44.5 (±29.6)	0.00	9.8 (±3.3)	10297.50 (±9050.8)	197400.0 (±98357.0)	12.6 (±4.1)
Malaria	Severe	13.1 (±12.2)	120827.6 (±244587.6)	6.7 (±4.0)	8649.6 (±6334.4)	155240.0 (±93505.0)	15.1 (±8.4)
	Simple	18.7 (±20.5)	2393.8 (±2748.4)	8.3 (±3.6)	10091.5 (±5721.4)	184402.1 (±109528.7)	14.0 (±6.0)
	Negative	44.5 (±29.6)	0.00	9.8 (±3.3)	10297.5 (±9050.8)	197400.0 (±98357.0)	12.6 (±4.1)
Total		20.7 (±22.2)	36889.3 (±141660.9)	9.4 (±3.5)	9696.5 (±6401.1)	177660.0 (±103481.8)	14.1 (±6.6)

α: p = 0.419; β: p = 0.404; ¢: p = 0.366; §: p = 0.575.

Table 2. GE results, Gender, malaria classification and biochemical parameters.

Parameters		ASAT (UI/L)	ALAT (UI/L)	CRP (mg/L)	Créatinine (µmol/L)	Hcy (µmol/L)€£
Sex	Male	24.4 (±3.6)	22.4 (±4.9)	53.6 (±54.8)	75.9 (±77.8)	14.1 (±5.4)
	Female	29.6 (±28.9)	26.4 (±32.1)	102.4 (±146.1)	192.7 (±491.8)	14.2 (±7.3)
Thick smear results€	Positive	36.0 (±25.4)	16.6 (±7.1)	119.5 (±145.6)	51.1 (±12.2)	14.4 (±6.9)
	Negative	34.1 (±25.9)	27.4 (±28.9)	36.2 (±50.3)	218.9 (±510.3)	12.6 (±4.1)
Malaria£	Serious	18.0 (±3.2)	21.7 (±5.6)	140.9 (±135.3)	44.3 (±6.1)	15.1 (±8.4)
	Simple	24.0 (±4.3)	11.6 (±6.1)	112.3 (±156.0)	55.2 (±13.6)	14.0 (±6.0)
	Negative	34.1 (±25.9)	27.4 (±28.9)	36.2 (±50.3)	218.9 (±510.3)	12.6 (±4.1)
Total		34.5 (±24.2)	25.0 (±25.6)	83.8 (±120.2)	151.8 (±397.4)	14.1 (±6.6)

€: p = 0.452; £: p = 0.419.

4. Discussion

The present study assessed the influence of *Plasmodium falciparum* infection on plasma level of homocysteine in people from Burkina Faso. An elevated plasma levels of Hcy was found in patients with severe malaria (15.1 ± 8.4 µmol/L) compared to those with uncomplicated malaria (14.0 ± 6.0 µmol/L) or negative controls for malaria (12.6 ± 4.1 µmol/L).

Our findings are in line with those of Chiellemi *et al.* [16] who reported a high level of plasma homocysteine in all subjects with *P. falciparum* malaria and correlated positively with the disease severity and the number of parasites. This increase could be due to the oxidative stress exerted by the *P. falciparum* infection and requires higher consumption of glutathione [16] [28] [29]. Altogether the hyperhomocysteinemia in patients with severe malaria in the present study suggests routine dosing for plasma Hcy as a marker of malaria severity in symptomatic individuals.

Plasma levels of homocysteine in the present study were similar in both men (14.1 ± 5.4 µmol/L) and women (14.2 ± 7.3 µmol/L) although Simpore *et al.* [14] reported that plasma levels of total Hcy are particularly low in black females. Low homocysteinemia has been reported infertile women (6.8 ± 1.2 µmol/L) against high homocysteinemia in postmenopausal women (16.4 ± 6.6 µmol/L) in Burkina [15]. Women were predominant in our study population due to their proportion in the population of Burkina Faso [27], and their high attendance at health centers as well as their ease adhesion to research studies compared to men.

The homocysteinemia (12.6 µmol/L) found in the malaria negative controls of the present study is higher than the plasma concentration of homocysteine reported in Burkina (6.9 ± 1.3 µmol/L for men and 5.9 ± 1.9 µmol/L for women) [13] [14], and similar to the levels of 13.5 µmol/L found in Togo and 14.1 µmol/L in Benin [30]. In fact, it is well known that homocysteinemia varies according to methionine-rich diet or genetic polymorphisms of the enzymes involved in the homocysteine metabolism [14] [25]. A multidisciplinary approach thus fixing the food factor could better help to understand the influence of the infection with *Plasmodium falciparum* on the plasma concentration of homocysteine in Burkina Faso.

Chillemi *et al.* [16] reported that elevated level of plasma homocysteine was negatively correlated with hemoglobin levels and patient ages. However, no correlation was found between plasma homocysteinemia and hematological, biochemical, or socio-demographic parameters in the present study. The relatively low mean age (20.7 years, **Table 1**) of our study population is a factor to consider since homocysteinemia increases with age.

The serum levels of L-alanine aminotransferase (ALAT) and L-aspartate aminotransferase (ASAT) is a primary screening tool for detecting acute liver injury [31]. The mean values of transaminases in the present study suggest poor effect of homocysteinemia on liver function. CRP with an average of 83.8 g/L was overall elevated in our study population and suggests inflammation in most study participants. Elevated serum creatinine due to renal failure was also found in women (192.7 µmol/L mean). It is well known that infection with *Plasmodium falciparum* leads to a decrease in the hemoglobin level through the destruction of infected red blood cells [32]. A low hemoglobin level (6.7 ± 4 g/dl) was observed in patients with severe malaria in our study population.

Hyperhomocysteinemia is known to be a risk factor in the occurrence of cardiovascular disease, renal failure, and diabetes [33] [34] [35]. We report for the first time in Burkina Faso enzymatic assay of plasma homocysteine using routine biochemistry platform with the perspective of routine dosage of homocysteine in association with various pathologies. This will make it possible to investigate the divergences in the literature in the specific context of Burkina Faso. Indeed, it has been reported that the administration of products derived from folate as well as vitamins B6 and B12 leading to a drop in homocysteinemia has not proved their effectiveness in the occurrence of various pathologies [36] [37] [38]. Drugs long used against malaria (pyrimethamine, sulfadoxine) exploit the oxidative power that prevents the parasite from avoiding oxidation in the red blood cells. These oxidizing drugs are therefore able to destroy the anti-oxidative system of *plasmodium falciparum*. Pyrimethamine and many other antifolates bind to the parasite tetrahydrofolate dehydrogenase more tightly than to the host enzyme [39]. Parasites such as *Plasmodium falciparum* do not have dihydro-neopterin aldolase but can circumvent this obstacle by using another enzyme such as pyruvoyltetrahydropterin synthase [40]. Plasmodium can also import folate cycle

derivatives from the host for its own needs [41]. The antioxidant drugs used act to block certain enzymes that contribute to the formation of tetrahydrofolate. Blocking these enzymes prevents the development of *plasmodium falciparum* in the host cells. Molecules that can prevent the parasite from avoiding oxidation inside the red blood cell will therefore help to inhibit the parasite and limit its development in the host organism.

5. Conclusion

The present study suggests a tendency for the increased plasma concentration of homocysteinemia induced by *Plasmodium falciparum* infection. It opens up prospects for multidisciplinary studies to better define the influence of *Plasmodium falciparum* on homocysteinemia and its association with various pathologies.

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Author Contributions

Conceptualization: Noé Yaméogo, Florencia Wendkuuni Djigma and Jacques Simporé; Methodology: Noé Yaméogo, Alfred Rakissida Ouédraogo; Bapio Valérie Bazié, Alfred Rakissida Ouédraogo, and Jacques Simporé; Software, validation: Noé Yaméogo, Bapio Valérie Bazié and Jacques Simporé; Formal analysis: Noé Yaméogo, Alfred Rakissida Ouédraogo, Bapio Valérie Bazié; Investigation: Noé Yaméogo, Alfred Rakissida Ouédraogo, Bapio Valérie Bazié and Jacques Simporé; resources, Jacques Simporé; Data curation, writing-original draft preparation: Noé Yaméogo, Alfred Rakissida Ouédraogo and Jacques Simporé; Writing review and editing: Noé Yaméogo, Alfred Rakissida Ouédraogo, Bapio Valérie Bazié, Alfred Rakissida Ouédraogo, Florencia Wendkuuni Djigma, Jacques Simporé; Visualization, supervision: Jacques Simporé; Project administration: Jacques Simporé, Florencia Wendkuuni Djigma; Funding acquisition: Noé Yaméogo and Jacques Simporé. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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