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Changes in Liver Function Enzymes in *Plasmodium falciparum* Infected Malaria Patients in Ajeromi General Hospital, Lagos, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Authors UOO and KCO designed the study and wrote the protocol. Author UOO managed the literature searches, performed the statistical analysis and wrote the first draft of the manuscript. Authors UOO, IOA and OOB performed the laboratory analyses. All authors read and approved the final manuscript.

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ABSTRACT

Objective: This study is to determine the changes in liver function enzymes in *P. falciparum*-infected patients in Ajeromi ifelodun area of Lagos, Nigeria by examining changes in some liver enzymes: Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Alkaline phosphatase (ALP) obtained from newly diagnosed cases of malarial infection yet to be treated.
Study Design: Seventy (70) human subjects comprising of 50 *P. falciparum* malarial infected and 20 non-infected (control) subjects between 10-60 years were selected for this study. Malaria positive subjects were divided into three groups based on the number of parasite per µl. Those that had parasitaemia below 10,000 parasites per µl were considered a mild infection, those that had parasitaemia above 10,000 parasites per µl were considered severe infections and those with parasitaemia below 1,000 parasites per µl were considered a low infection. RDT test and

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microscopy was carried out to ascertain the presence of *P.falciparum.* They were grouped based on age group, sex and level of parasitaemia.

Materials and Methods: Blood samples were collected for the determination of *P. falciparum*, level of parasitaemia and liver function enzymes Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP). *P. falciparum* was determined by Rapid Diagnostic Test (RDT) and microscopy.

Results: There was a significant increase ($P < 0.001$) in the mean level of serum Aspartate Transaminase (AST), Alanine Transaminase (ALT) and a significant decrease in the mean level of alkaline phosphatase (ALP) in the *P. falciparum*-infected patients compared to the control subjects. AST level was found to be significantly higher ($P<0.001$) among age group (51- above) in the *P. falciparum* patients and significantly lower among age group (10-20) in the control subjects when compared to other age groups.

ALT level was significantly higher ($P < 0.001$) among age group (51- above) in the *P. falciparum* patients and significantly lower among age group (41-50) in the control subjects when compared to other age groups. ALP level was significantly higher ($P < 0.001$) among age group (41-50) in the *P. falciparum* patients and significantly lower among age group (10-20) in the control subjects when compared to other age groups. AST and ALT were found to be significantly higher ($P < 0.001$) in the high parasitaemia group when compared to the low and moderate parasitaemia group and they were also significantly higher in the moderate parasitaemia group than in the low parasitaemia group.ALP was significantly higher ($P < 0.001$) in the moderate parasitaemia group when compared to the low and high parasitaemia group and they were only marginally lower in the high than in the low parasitaemia group.

Conclusion: There was an elevated level of liver function enzymes in the *P. falciparum* patients than in the control subjects. This study shows that high parasitaemic patients are at greater risk of hepatic damage than the low parasitaemic group, hence early diagnosis and treatment of malaria are highly encouraged.

Keywords: P. falciparum; Aspartate Transaminase (AST); Alanine Transaminase (ALT); Alkaline Phosphatase (ALP); parasitaemia; dysfunction; Rapid Diagnostic Test (RDT).

1. INTRODUCTION

According to the World Health Organization, malaria is a significant public health problem in more than 100 countries of the world and causes an estimated 200 million infections each year, with more than 500 thousand deaths annually. Over 90% of these deaths occur in sub-Saharan Africa, where the disease is estimated to have killed one child in every 30 seconds [1]. In Nigeria, close to 96 million people are exposed to malaria, out of which 64 million get infected, and almost 300,000 deaths, reported annually [2]. Malaria poses a lot of challenges despite enormous government, foreign and donor partner efforts.

The prevalence and severity of malaria are higher among children and pregnant women than in any other groups [1,3]. The malaria parasite vector is the female Anopheles mosquito [4]. The disease is caused by protozoan parasites of the genus *Plasmodium*. Four species of the *Plasmodium* parasite can infect humans. The most serious forms of the disease are caused by *P. falciparum* [5]. *P. vivax* and *P. ovale* infections show respectively an incubation period of 13 and 17 or more days and again fever occurs every 48 hours. The fourth parasite, *P. malariae,* causes chronic, often low grade, infection. The malaria infection is common in localised areas in the tropics. This infection has an incubation period of 28 days or longer and fever occurs every 72 hours [6]. The infection may persist for 50 years or more but is often without serious morbidity [7].

Usually, people get malaria from bites of an infective female *Anopheles* mosquito. Only *Anopheles* mosquito can transmit malaria and they must have been infected through a previous blood meal taken on an infected person [8]. When a mosquito bites an infected person, a small amount of blood is taken, which contains microscopic malaria parasites. When the mosquito takes its next blood meal, these parasites mix with the mosquito's saliva and are injected into the person being bitten. Malaria parasites multiply within the red blood cells causing symptoms that include fever, nausea, arthralgia, shivering, convulsion, haemoglobinuria and retina damage [9]. Malaria parasites head to the liver after arriving in a human body

and changes into a new form that can infect red blood cells and begin to reproduce. The sporozoite enters the bloodstream and migrates to the liver. In the liver, they multiply into merozoites which infect and rupture the liver cells in an attempt to escape back into the bloodstream where infection continues. Malaria parasites invade the immune system when they move from the liver to the red blood cells. The invasion of liver cells by the sporozoite form of the malarial parasites can cause organ congestion, sinusoidal blockage and cellular inflammation [10]. The parasites destroy the liver cell they occupy and make it detach from its neighbour. When these happen, it causes the parenchymal (transaminases) and membraneous (alkaline phosphatase) enzymes of the liver to leak into the circulatory system leading to increased enzyme activity [11].

The severity of malaria infection has been linked with the increase in the level of liver enzymes in the body [12,13]. As a result of the high level of complication and death of children due to malaria infection, there is need to evaluate the extent of hepatic functions in malaria cases so that there will be proper management of malaria infection and its associated complication [14]. This study is to determine the changes in liver enzymes in *P. falciparum* infected patients in Ajeromi ifelodun area of Lagos, Nigeria by examining changes in some liver enzymes: AST, ALT and ALP obtained from newly diagnosed cases of malarial infection yet to be treated.

2. MATERIALS AND METHODS

2.1 Study Laboratory and Period

This research was conducted in the Nigerian Institute of Medical Research Laboratory, Department of Biochemistry, Yaba, Lagos between August 2015 and January, 2016.

2.2 Subject's Selection

Seventy (70) human subjects comprising of 50 *P. falciparum* malarial infected and 20 non-infected (control) subjects between 10-60 years were selected for the study. The place where this study was conducted is a peri-urban area with a high episode of malaria infection. Selection and pre-qualification were done by simple random sampling of males and females presenting for malaria parasite test at Ajeromi General Hospital Laboratory, Lagos State, Nigeria, with a history of fever (temperature > 37°C), headache and malaise within a period of 2- 8 days and who were subsequently confirmed to be *Plasmodium falciparum* malaria positive by RDT Kits (Rapid Diagnostics Test) and later microscopic examination of Giemsa Stained thin and thick blood slide.

2.3 Patient's Selection Criteria

Based on the following selection criteria, 50 patients found to be qualified for participation in the study were selected. The ages of patients ranged from 10-60 years. Patients whose case history showed a concomitant presentation with the following conditions; pregnancy, renal diseases, liver diseases including cirrhosis, hepatitis, obstructive jaundice, alcoholism, cancer, metabolic bone diseases, gastrointestinal tract infection, protein-energy malnutrition, diabetes, heart failure, sickle cell, HIV/AIDS were excluded from the study. This is because these conditions are associated with significant changes in serum alkaline phosphatase, alanine and aspartate transaminases activities and other enzymes of interest.

Similarly, patients on self-medication with any antimalarial drug before presentation were also excluded from the study. Twenty (20) subjects in apparent good health and malaria parasite negative were included as control individuals, however, presence or absence of malaria infection was confirmed using Giemsa Stain procedure. Consent was sought and obtained from the subjects. The malaria patients and control subjects were sex - and age-matched.

2.4 Collection of Blood Samples

Blood sample collection was carried out through the medical officers of the Ajeromi General Hospital. A 5 ml whole blood samples were drawn with 10 ml syringe from subjects by venipuncture into Lithium Heparin and EDTA vacutainer tubes to prevent blood clot. Each sample was centrifuged at 3000 g for 10 min at room temperature (about 29-30°C) to obtain the plasma. The plasma was removed from the mixture using a micropipette and placed in a separate labelled container and stored frozen until required for analysis which was done within 48h and the biochemical assay was carried out within 48 h of collection.

2.5 Parasitological Examination

Randomization was performed through the selection of patients with the diagnosis of malaria by thick and thin blood smearing.

The presence and density of *P. falciparum* in each blood sample was determined from Giemsa-stained thin and thick blood films. Thick blood film was prepared on the slide from the whole blood collected from each patient. The slide was stained with 3% Giemsa' stain [4] and left for about 45 min, after which the slide was washed and allowed to dry. The slide was mounted on the light microscope and screened for the presence of malaria parasite. A slide was considered negative when no parasite was found after the screening of 200 fields. For those slides that were positive the number of parasites counted per 200 white blood cells was used to calculate parasite density based on 8000 leukocytes per µl of blood. Parasitaemia was calculated using the formula:

$$\frac{\text{No. of parasite} \times 8000}{\text{Count WBC } 200}$$

Positive smears were grouped into two:

Low parasitaemia, with parasite density of <1000 asexual forms per ml of blood.

High parasitaemia, with parasite density of > 10,000 asexual forms per ml of blood.

2.6 Diagnosis of Malaria Parasite Using a Rapid Diagnostic Kit Test

Malaria *Plasmodium falciparum* was screened for using commercially prepared malaria rapid test kit. The test device is a rapid chromatographic immunoassay for the qualitative detection of circulation of *Plasmodium falciparum* in whole blood.

2.6.1 Procedure

The procedure was as described by the manufacturer of the kit (Acon Laboratories, Inc.). 20 ul of whole blood was pipette into the clean labelled test tube, 120 ul of buffer solution was added and waited for 1minutes, contents in the test tube was mixed, 140 ul of the mixed-blood sample and buffer solution was pipette into specimen well on test device and wait for the colour line(s) to appear. The result was read at 15 minutes. Interpretation of results: for positive result, two distinct coloured lines should appear,: one line was in control region and another line was in test region. For negative result: only one coloured line appeared in the control region, result was invalid if control line fails to appear.

2.7 Microscopic Diagnosis of Malaria Parasite Using Thick and Thin Stained Blood Film

2.7.1 Thick and thin stained blood film

Thick blood film was made and stained using Giemsa's staining technique for malaria parasite detection and malaria parasite count. However, thin blood film was also made and stained with Giemsa's staining technique for plasmodium species identification. The number of asexual *P. falciparium* and other species per 200 leukocytes were counted and if ten or more parasites were identified, then the number was recorded, a blood sample was regarded as negative if the examination of thick films failed to show the presence of asexual parasites. The parasite count in relation to the leukocyte count was converted to parasite per micro litre of blood using this mathematical formula;

$$\frac{\text{Number of parasites}}{\text{Number of leukocytes}} \times \text{Total WBC count} = \text{Parasite per micro litre of blood.}$$

2.7.2 Procedure for staining thick blood film

The procedure used was described by Cheesbrough (2005), 3% of stock Giemsa stain was diluted in buffered water immediately before use. Thick blood film was made on clean grease free glass slide, allowed to air-dry and stained with prepared Giemsa stain for 30 mintues. Stained slide was rinsed in clean water and allow air-drying before examined under microscope using X100 objective lens. Chromatin of malaria parasite stained dark red and cytoplasm stained blue with Giemsa's stain. The diagnosis of malaria was made with certainty on identification of malaria parasite together with other symptoms associated with malaria infection. The presence of malaria parasite, identification of the species of human parasites and relative malaria parasite count in each blood sample was determined from Giemsa stained thick films and thin blood film. Malaria Parasitaemia was confirmed by microscopic examination using X100 objective lens (oil immersion lens).

2.7.3 Procedure for staining thin blood film

Thin blood film was made on clean grease free glass slide and stained using Giemsa's staining technique; the procedure was described by Cheesbrough (2005); the film was allowed to air

dry and fixed with methanol, allowed to dry and stained using Giemsa stain for 30 minutes. The slide was diluted with buffered distilled water and allowed to stain for 10 minutes. Slide was rinsed with water; back of the slide was cleaned with damped cotton wool in methylated spirit. The slide was allowed to air dry and examined under microscope using X100 objective lens.

2.7.4 Estimating and grading of parasitaemia

Malaria Parasitaemia was graded as + = 1 – 10 parasites per 100 thick film field, ++ = 11 – 100 parasites per 100 thick film field, +++ = 1 – 10 parasites per single thick film field, ++++ = more than 10 parasites per single thick film field after staining for 30 minutes. Identification of the species of human parasites in the blood films was carried out according to WHO method. A slide was scored as negative when 100 high power fields had been examined for about 30 minutes without seeing any parasites. The amount of relative parasite count in positive smears was done using a simple code from one to four crosses (+ - ++++) [15].

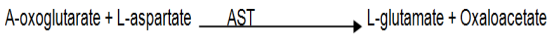
2.8 Liver Enzymes Assays

Aspartate and alanine transaminases were assayed by colorimetric method [16] using Roche model Diagnostic Reflotron. Serum total alkaline phosphatase activity was assayed using the thymolphthalein monophosphate method [17].

2.8.1 Determination of plasma aspartate aminotransferase

The assay was carried out according to the method described by Reitman et al. (1959).

Procedure:

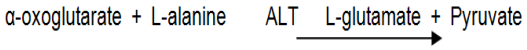


Test tubes were set in the following procedure: blank and Assay. 100 µl of distilled water was added to the blank test tube while 100µl of plasma was added to the assay test tubes. 500µl of Reagent 1 (R1) (phosphate buffer, L-aspartate, and α-oxoglutarate) was added to the blank and assay test tubes. The setup was mixed and incubated for 30 minutes at 37°C. 500 µl of Reagent 2 (R2) (2,4-dinitrophenylhydrazine) was added to both the blank and assay test tubes and allowed to stand for 20 minutes at 25°C. 5 ml of 0.4 mol/l sodium hydroxide was added to the test tubes. The absorbance of the sample (assay) was read against the reagent blank after 5 minutes at 546 nm wavelength.

2.8.2 Determination of alanine amino-transferase

The assay was carried out according to the method described by Reitman (1959).

Procedure:



Test tubes were set in the following procedure: blank and Assay. 100µl of distilled water was added to the blank test tube while 100 µl of plasma was added to the assay test tubes. 500 µl of Reagent 1 (R1) (phosphate buffer, L-alanine, and α-oxoglutarate) was added to the blank and assay test tubes. The setup was mixed and incubated for 30 min at 37°C. 500 µl of Reagent 2 (R2) (2,4-dinitrophenylhydrazine) was added to both the blank and assay test tubes and allowed to stand for 20 min at 25°C. 5 ml of 0.4 mol/l sodium hydroxide was added to the test tubes. The absorbance of the sample (assay) was read against the reagent blank after 5 min at 546 nm wavelength.

2.8.3 Determination of alkaline phos-phatase

Plasma Alkaline Phosphatase was determined according to the method described by Babson et al. (1966).

Test tubes were set in the following procedure: Standard and Assay. 1ml of distilled water was added to both the standard and assay test tube; 50µl of plasma was added to the assay test tubes and 50 µl of the standard added to the standard test tube. One drop of phenolphthalein monophosphate was added to both the standard and assay test tubes and allowed to stand for 20 minutes at 25°C.The absorbance of the sample (assay) was read against the reagent blank after 5 min at 546 nm wavelength.

2.9 Statistical Analysis

The results were expressed as Mean ± Standard Deviation. Data obtained were analysed using student t-test to compare means. Analysis was performed using computer database software from the statistical package for social sciences (version 16.0 SPSS). A p-value< 0.05 was

considered statistically significant in all clinical comparisons at 95% confidence interval.

3. RESULTS

Table 1 shows a significant increase in the mean level of serum Aspartate Transaminase (AST), Alanine Transaminase (ALT) and a significant decrease in the mean level of Alkaline Phosphatase (ALP) in the *P. falciparum* infected patients compared to the control subjects.

Table 2 shows the level of some liver function enzymes in *P. falciparum* patients and control subjects based on sex. AST and ALT levels was found to be significantly higher ($P < 0.001$) in the female and male *P. falciparum* patients than in the control subjects. ALP was significantly lower in the female and male *P. falciparum* patients than in the control subjects.

Table 3 shows the level of some liver enzymes in *P. falciparum* patients and control subjects based on age. AST level was found to be significantly higher among age group (51 and above) in the *P. falciparum* patients and significantly lower among age group (10-20) in the control subjects when compared to other age groups. ALT level was significantly higher ($P < 0.001$) among age group (51 and above) in the *P. falciparum* patients and significantly lower among age group (41-50) in the control subjects when compared to other age groups. ALP level was significantly higher among age group (41-50) in the *P. falciparum* patients and significantly lower among age group (10-20) in the control subjects when compared to other age groups.

Table 4 shows the mean level of liver enzymes activities at different levels of parasite density or parasitaemia in *P. falciparum* malaria patients and control subjects. AST and ALT were found to be significantly higher ($P < 0.001$) in the high group when compared to the low and moderate and they were also significantly higher in the moderate than in the low group.ALP was significantly higher ($P < 0.001$) in the moderate when compared to the low and high and they were only marginally lower in the high than in the low parasitaemia group.

4. DISCUSSION

The liver is very important in the body and its impairment needs to be detected early and managed properly. The pathogenesis of this parasite infection involves the liver stage where infected sporozoites invade and multiply in the hepatocytes and an erythrocyte stage where merozoites cause the destruction of the infected red blood cells prior to their differentiations into male and female gametocytes leading to significant alterations in host hepatocyte physiology and morphology.

From this study, evidence shows that malarial infection can induce changes in liver enzyme activities. This result clearly shows that there was a significant difference ($P < 0.001$) in the levels of the liver enzymes (ALT, AST and ALP) in malaria parasite infected patients when compared with the non-malaria parasite infected (control) subjects. The normal healthy values for serum ALT, AST and ALP as estimated by the

Table 1. Level of some liver function enzymes in *P. falciparum* patients and control subjects

Liver functions Parameters	Sample (mean± SD)	Control (mean± SD)
AST(U/l)	79.94±42.92	63.36±48.51
ALT(U/l)	24.21±12.46	16.65±12.81
ALP(U/l)	34.41±11.98	65.24±20.89

Table 2. Level of some liver function enzymes in *P. falciparum* patients and control subjects based on sex

Liver functions Parameters		Sample (mean± SD)	Control (mean± SD)
AST(U/l)	Male	89.84 ± 37.98	79.19 ± 55.24
	Female	71.28 ± 46.27[c]	35.67 ± 11.62[d]
ALT(U/l)	Male	26.05 ± 11.45	19.22 ± 15.68
	Female	22.6 ± 13.44[c]	12.14 ± 3.61[d]
ALP(U/l)	Male	34.31 ± 10.14	59.94 ± 20.39
	Female	34.5 ± 13.71[c]	74.52 ± 21.02[d]

(a, b) Values with superscript in the same row for a particular gender are significantly different
(c, d) Values with superscript in the same column for a particular group are significantly different

Table 3. Level of some liver enzymes in *P. falciparum* patients an control subjects based on age

Parameters	Age groups	Samples (mean±SD)	Control (mean±SD)
AST(U/l)	10-20	72.11 ± 42.41	36.13 ± 0
	21-30	91.68 ± 43.11	84.28 ± 97.01
	31-40	71.18 ± 47.38	72.51 ± 39.62
	41-50	82.36 ± 43.03	47.65 ± 0
	51and above	104.82 ± 69.03	59.93 ± 51.14
	Total	**85.32 ± 49.18**	**63.36 ± 48.51**
ALT(U/l)	10-20	13.83 ± 7.57	17.17 ± 0
	21-30	27.06 ± 11.86	27.09 ± 28.35
	31-40	21.74 ± 10.77	12.56 ± 5.32
	41-50	23.76 ± 12.74	11.68 ± 0
	51and above	33.67 ± 21.66	14.99 ± 11.39
	Total	**25.48 ± 14.07**	**16.65 ± 12.81**
ALP(U/l)	10-20	37.26 ± 17.57	102.12 ± 0
	21-30	40.42 ± 15.79	40.02 ± 25.38
	31-40	30.96 ± 7.82	63.48 ± 15.62
	41-50	41.01 ± 11.43	63.48 ± 0
	51and above	31.05 ± 11.78	69 ± 13.8
	Total	**35.76 ± 12.71**	**65.24 ± 20.89**

Table 4. Mean level of liver enzymes activities at different levels of parasite density in *P. falciparum* patients and control subjects

AST(U/l)	Low	73.14 ± 8
	Moderate	105.18 ± 10
	High	111.94 ± 6
	Total	**96.19 ± 24**
ALT(U/l)	Low	18.88 ± 8
	Moderate	29.89 ± 10
	High	40.55 ± 6
	Total	**28.89 ± 24**
ALP(U/l)	Low	33.81 ± 8
	Moderate	39.2 ± 10
	High	32.66 ± 6
	Total	**35.77 ± 24**

Tabulated values are expressed as Mean ± Standard Deviation (±S.D)

International Federation of Clinical Chemistry (IFCC) are in the reference ranges of 10-40, 8-20 and 38-94IU/L, respectively. The various enzyme levels increased with increase in malaria parasite density. This observation demonstrates that the hepatic stage of the parasite's life cycle in its human host is accompanied by significant perturbation in the hepotocyte membrane leading to leakage of the liver enzymes into a general circulation.

There was also a significantly ($P < 0.001$) higher enzyme levels (AST and ALT) in the infected male subjects when compared with their female counterparts. A previous study by Uzoegwu and Onourah [18] reported a percentage malaria parasite infection rate of 51.1% in males and 41.4% in females, and this higher susceptibility of males to malaria parasite infection than females could be responsible for the higher enzyme activities observed in the infected male subjects.

This study showed an increased level of ALT, AST and ALP with age, as the age group (51 and above) and (41-50) showed a significantly higher level of these liver enzymes. This could be that malaria confers some level of hepatic compromise with age. It is also a source of concern among old people cause it could mean that this group of people when infected with *P. falciparum* might have a high likelihood of developing hepatic damage or it could also be that the liver being the major site of drug

metabolism, might have been exposed over time to prolong drug usage by adults leading to progressive damage of the liver in adult patients. This is still subject to further research.

The serum ALP levels were significantly reduced in the high parasitaemia group when compared with the moderate and low groups. A previous study reported a reduction in the serum ALP in malaria patients [19], which was probably a result of intervention of malaria parasite in the synthesis of protein. The invasion and development of the malaria parasite into the liver during the life cycle may be responsible for liver dysfunction by causing organ congestion, cellular inflammation, and sinusoidal blockage [20]. The increase in the serum ALT and AST in the high and moderate parasitaemia group when compared with the low group in this study shows that malaria parasite infection may be responsible for the increase in the liver enzymes, which may lead to liver dysfunction. This agrees with a previous study that showed that *P. falciparum* infection may be responsible for the increase in the liver enzymes [21]. The increase in serum ALT and AST in malaria positive patients could be as a result of leakage of these enzymes from the liver, as a result of damages to liver cell during the liver stage of the life cycle of malaria parasite. The ALT and AST level were higher in the group with high parasitaemia as compared with the moderate group which is an indication that the level of liver dysfunction may be determined by the level of parasitaemia in the body. Findings in this study also agree with the previous studies which showed a positive correlation between the level of liver dysfunction and parasitaemia [12,13].

The ALP level was significantly higher in the moderate group than in the low parasitaemia group which is also a positive correlation between liver dysfunction and level of parasitaemia, though it was also higher than in the high group. The factors that may be responsible for this high ALP level in the moderate group to that of the low group is not known, therefore, there is a need for further studies to ascertain this.

5. CONCLUSION

The findings of this study show that there was an elevated level of liver function enzymes (ALT and AST) in the *P. falciparum* patients than in the control subjects and a reduced level of ALP in the *P. falciparum* patients than in the control subjects. This study shows that high parasitaemic patients are at greater risk of hepatic damage than low parasitaemic group, hence early diagnosis and treatment of malaria is highly encouraged.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standard.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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