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*Original Research Article*

# Malaria Parasitaemia and Effect on Liver Enzymes

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**Abstract**

**Malaria is one parasite that is responsible for fever in tropical countries. The genus *plasmodium* is an obligate intra-erythrocyticprotozoa which causes malaria. Malarial involvement with liver is now a known case with its specific biochemical aberrations. The aim of this study was to determine the effects of density of *Plasmodium falciparum* parasitaemia on serum liver enzymes. It was a cross sectional study of One thousand (1000) children comprising of Six hundred and ninety four (694) children with malaria taken as the test group while 306 children that had no malaria were regarded as the control group. Blood samples were collected from them and examined for malaria and Liver enzymes such as ALT, ALP and GGT. The data obtained from the study were analyzed using GraphPad Prism Version 8.0.2.263. Result gotten from the study showed that the levels of the liver enzymes reduces as the parasite density increases from moderate to high. Post hoc analysis also showed a significant difference in the levels of ALT and ALP but no significant difference in the level of GGT. This study has demonstrated that higher density of plasmodium could bring about reduction in the levels of liver enzymes. It is therefore recommended that liver function test be carried out in chronic malaria infestation to aid effective treatment.**

**Keywords:** Malaria, Plasmodium, Liver enzymes

## INTRODUCTION

Malaria is one parasite that is responsible for fever in tropical countries (Dennis *et al*., 2005). Malaria manifests with non-specific symptoms; a feeling of lacking a sense of well-being, muscle pains, headache, fatigue, and abdominal discomfort, which bring about the onset of fever are all symptoms which are seen in minor viral illnesses. Malarial paroxysm is characterized by a spike in fever, chills, and rigors occur as the infection progresses. These symptoms are not usual and may suggest infection with *Plasmodium vivax* or *Plasmodium. Ovale* (Dennis *et al*., 2005). At first the fever will be irregular (infection with falciparum malarial may never bring about a regular symptom); there is usually a rise in temperature above 40$^{o}$C with tachycardia and sometimes delirium in individuals with low immune system and in children (Dennis *et al*., 2005). Any of the species may lead to childhood febrile convulsion, falciparum malarial brings about generalized seizures and may bring about the development of cerebral disease. (Dennis *et al*., 2005).

The genus *plasmodium* which is an obligate intraerythrocytic protozoa which causes malaria. Malaria has four species which are: P. *falciparum*, P. *ovale*, P. *malariae* and P. *vivax*. P. *knowlesi*, a fifth specie previously found in monkeys, has also been shown to infect humans. (Dennis *et al*., 2005).The malaria found in the tropicals is usually implicated with either P. *falciparum* or P. *vivax*, and most malaria linked to deaths are due to P. *Falciparum (*Warrell *et al*., 1990; Ogunledun *et al*., 1991; Miguel *et al*., 2006) 5-7% of infection is usually caused by what is known as mixed infection is caused by more than one species of plasmodium.*(*Warrell *et al*., 1990). Infection with plasmodia is via the bite of female *Anopheles* mosquito, one can also get infected through

exposure to infected blood products (Known as transfusion malaria) and from mother to child (congenital transmission). Most cases of malaria infection recorded in industrialized countries are seen in travellers, immigrants, or military personnel returning from areas endemic for malaria (*imported malaria*). Interestingly, transmission locally with malaria occurs through the bite of mosquito (*indigenous malaria* which is malaria that is gotten and transmitted within a locality rather than coming or imported from somewhere else) (Onwujekwe *et al*., 2000). 50% of all expenditures on curative diseases annually in Nigeria are used for malaria treatment and prevention (Onwujekwe *et al*., 2000). In Nigeria malaria is considered a serious public health challenge. Children, pregnant women and the elderlies are more at risk of being infected with malaria. Over 50% of Nigeria's 140 million population is faced with one case of malaria every year. (Ezejie *et al*., 1991). Recently malaria vectors has acquired resistance to therapies and this has made the treatment of malaria challenging, while cases of resistance by the parasites are increasing by the day. New therapies are not properly applied because of fear of lack of effectiveness (Ezejie *et al*., 1991). Statistics show that 3-3.5 million annual deaths worldwide take place due to malaria infection (Rigler and Lake, 1993; Harshad, 2005). Statistics also showed that malaria kills one child every 30 seconds and about 3000 children daily (Anand *et al*., 1992). Children between age 5 years and below are more prevalence in these situations. 90% of the deaths annually that occur in rural sub-Saharan Africa are attributed to malaria infestation (Miguel *et al*., 2006). According to epidemiological studies, at least 20% of all deaths in children under five in Africa are due to malaria (Mishra *et al*., 1992).

Malarial involvement with liver is now a known case with its specific histopathological aberrations. It has been reported that cases with altered liver function test, results to hepatic failure and hepatic encephalopathy (Egwunyenga *et al*., 2004).

*Plasmodium* parasite affects the organs of the body such as brain, kidney, liver, lungs, central nervous system and spleen etc. Ogbadoyi and Tsado (2009) in their study reported that Hepatic dysfunction is 7.15%at Minna, Niger State, Nigeria. Liver involvement in malaria infection has become a common case inpatients with severe malaria and sometime manifest as jaundice which is an increase serum bilirubin level, hepatomegaly, rise in liver enzymes like aspartate aminotransaminase/ alanine transaminase; some cases show reduction in albumin and an increase in prothrombin time. There is usually specific histopathological alterations and changes in liver function test parameters, (fulminant hepatic failure and hepatic encephalopathy) (Rajesh *et al*., 2003). Some researchers also reported that malaria hepatitis is characterized by increased transaminase levels to more than three times the upper limits of normal and alkaline phosphatase (Bhalla *et al*., 2006).

The previous studies failed to correlate the changes in serum level of hepatic biochemical parameters with the density of falciparum parasitaemia. This study is therefore carried out to determine the effects of density of *Plasmodium falciparum* parasitaemia on serum liver enzymes. This is with a view to correlate degree of parasitaemia of *Plasmodium falciparum* with severity of hepatic injury.

## MATERIALS AND METHODS

### Study Design

This was a cross sectional study where the subjects were randomly selected. The study was carried out among children attending Palmars, Omega Children Hospital and Braithewait Memorial Specialist Hospital (BMSH) and schools (Early Breed Group of Schools, St Francis Nursery and Primary school and Staff Nursery and Primary school) in Port Harcourt, Rivers State. One thousand (1000) children were included in this study. Six hundred and ninety four (694) children had malaria and were regarded as test group while 306 children had no malaria were regarded as the control group.

The sample size was derived using the following formular: $N= Z^2 (PQ) /D^2$(Araoye, 2003).

### Study Location

The study was carried out among children attending Palmars, Omega Children Hospital and Braithewaite Memorial Specialist Hospital (BMSH) and schools (Early Breed Group of Schools, St Francis Nursery and Primary school and Staff Nursery and Primary school) in Port Harcourt, Rivers State. Port Harcourt is situated at latitude 4º 47´ 21´´ N and longitude 6º 59´ 54´´. One thousand (1000) children were included in this study. Six hundred and ninety four (694) children had malaria and were regarded as test group while 306 children had no malaria were regarded as the control group.

### Eligibility Criteria

### Inclusion criteria

The children included in the study include those within the age range of 1-10 years who had malaria parasitaemia with no history of liver disease and were not on any anti-malarial drug. Controls group were children who were not infected by malaria parasite and who had no history of any liver disease after laboratory trials by subjecting them to hepatitis B and C screening.

**Exclusion Criteria**

The subjects that were excluded in this study were all adults and individuals above 10 years of age irrespective of their health status, all malaria infected children on anti malaria medication prior to commencement of this study and hepatitis free subjects.

**Ethical Consideration and Informed Consent**

The Ethics Committee of the Rivers State Ministry of Health, Port Harcourt, Nigeria approved the protocol for this study. Informal consent was obtained from the parents of the children and the institutional authorities.

**Subject Selection**

Subjects having ensured that they met the criteria that made them suitable for inclusion in the study were selected randomly using a numbering style as described by some researchers (Biambo *et al*., 2021; Catherine *et al*., 2021; Diorgu *et al*., 2021).

**Sample Collection**

About 10 ml of blood samples were collected through the vein with disposable hypodermic syringe. About 5ml of which was dispensed into ethylene diethyl tetracetic acid (EDTA) bottle for malaria parasite test while 5ml was used for Liver function tests using total bilirubin, conjugated bilirubin and unconjugated bilirubin, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and gamma glutamyltransferase as parameters.

**Laboratory Methods**

**Blood film preparation (WHO, 1999; Cheesbrough, 2006)**

**Thin and thick film preparation**

Each blood was mixed thoroughly and gently. A drop of blood was placed at the centre of a clean grease free glass slide and another drop of blood at the right side of the same slide with the aid of a Pasteur pipette. Using a smooth edged slide spreader, the drop of blood was spread to make a thin film. The end of a Pasteur pipette was used to spread the drop of blood to make an even thick smear. This was allowed to air dry before staining.

**Staining Thin and Thick films using Giemsa's stain**

The dried thin film was fixed in methanol. This was then stained with the thick film using Giemsa's stain. 3% solution of Giemsa stain was made and the films were stained for 30 minutes. The back of each slide was blotted with cotton wool and place in the draining rack for drying. The films were examined using x100 Objective lens, (Oil immersion). The presence of malaria parasite was done using the thick blood films while the identification of the species was done using thin blood films. A slide was scored as parasite seen when 100 per high power fields had been examined without seeing any malaria parasite.

**Estimation of Parasite Density using Quantitative Method.**

Relative malaria parasite count in each blood sample was determined as described by Cheesbrough (2006).

**Counting of Percentage (%) Parasitized red cell using thin blood film**

The number of parasitized red cells was counted in about 4 fields (250 red blood cells per high power field), to get approximately 1000 cells. This was then divided by 10. This gave the percentage parasitized red blood cells.

**Counting Parasite numbers per microlitre of blood**

The number of asexual parasites present in each thick blood film was counted against 100 white blood cells. This was multiplied by the standard total white blood cells count (8000).

One hundred (100) white blood cells were counted while estimating the number of parasites (asexual) in each thick field covered.

**Calculations**

Number of parasites/ µl of blood

$$\text{Total } \frac{\text{WBC} \times \text{Number of asexual parasites}}{100 \text{ (Number of WBC)}}$$

**Biochemical Determinant**

**Alanine aminotransferase (ALT) (Enzymatic method Reitman and Frankel, 1957).**

Alanine aminotransferase estimation is used for the

determination of alanine aminotransferase in serum.

**Principle**

Alpha oxoglutarate + L-alanine. (GPT) → L-glutamate+ pyruvate. Alanine aminotransferase is measured by monitoring the concentration of pyruvate hydrazones formed with 2,4-dinitrophenylhydrazine.

**Procedure**

One hundred microlitres (100µl) of sample was pipette into a test tube. Five hundred microlitres (500µl) of buffer (phosphate buffer, L-alanine and alpha-oxoglutarate was added to the test tube as well as reagent blank test tube and mixed. One hundred micrilitres (100µl) of distilled water was added to reagent blank test tube, there were mixed and incubated for 30minutes at 37$^{o}$C. Five hundred microlitres (500µl) of 2, 4-dinitrophenylhydrazine was added to both test tube, mixed and was allowed to stand for 20minutes at 20 to 25$^{o}$C. Five thousand microlitres (5000µl) of sodium hydroxide was added to both test tubes and mixed. Asorbance of the solution was read photometrically against the reagent blank after 5minutes at 546nm

**Calculation of result**

The activity ALT in the serum was obtained from the ALT activity table.

**Alkaline phosphatise (ALP) (Phenolphthalein Monophosphate Substrate method by Englehardt *et al*., 1970)**

Alkaline phosphatase estimation is used to determine alkaline phosphatase in serum or plasma.

**Principle**

Serum alkaline phosphatase hydrolyses a colorless substance of phenolphthalein monophosphate giving rise to phosphoric acid and phenolphthalein which at alkaline pH values turns into pink color that can be photometrically determined.

**Procedure**

One hundred microlitres (100µl) of water was dispensed into 2 test tubes. Fifty microlitres (50µl) of phenophatein monophosphate is added into the tubes. They were mixed and incubated at 37$^{o}$C for 5 minutes. One hundred microlitres (100µl) of sample and standard was added into the test tubes and these were incubated at 37$^{o}$C for 20minutes. Five thousand microlitres (5000µl) of the colour developer was added into the test tubes. Absorbance of the solution was read photometrically at 550nm against water as blank.

**Calculationof result**

Alkaline phosphatase (u/l) =

$$\frac{\text{Absorbance of test} \times \text{standard concentration}}{\text{Absorbance of standard}}$$

**Gamma-glutamyltransferase (GGT) (5-amino-2-nitrobenzoate method by Szasz and Bergmeyer, 1974).**

**Principle**

The enzyme gamma glutamyl aminotransferase (GGT) transfers a gamma glutamyl group from the substrate L-gamma-glutamyl-4-nitroaniline to glycylglycine at pH 7.8
L-gamma-glutamyl-4-nitroaniline = glycylglycye → 4-nitroaniline + gamma-glutamylglycylglycine.

**Procedure**

One hundred microlitres (100µl) of sample was put into a cuvette. One thousand microlitres (1000µl) of buffer/glycerine (Tris buffer, Glycerine and L- gamma-glutamyl-3-carboxy-4-nitroanilide was added into the test tube and mixed properly. Initial absorbance was read and timer started simultaneously. The solution was read again after 1, 2 and 3 minutes at 405 nm.

**Calculation of result**

Gamma-glutamyltranferase (u/l) = Absorbance of test x 1158.
1158 (Multiplication factor) =

$$\frac{\text{Activity of GGT standard}}{\text{Absorbance of GGT standard}}$$

**Statistical Analysis**

The data obtained from the study were analysed using the GraphPad Prism Version 8.0.2.263. The data were expressed as mean and standard deviation. Comparison of the means was done using the one-way analysis of variance (ANOVA). The Tukey comparison test was used to verify significant differences between the groups at $P<0.05$.

**Table 1.** Mean Parasite Density/µl of blood and the Corresponding Liver Function Parameters

| Parameters | Parasite Density | Parasite Density | Parasite Density |
|---|---|---|---|
| **<1000/µl>1000 ≤ 9999/µl >10000/µl** | **(873.8 ± 30.44)** | **(3248 ± 109.31)** | **(24813.8 ± 877.22)** |
| ALT (iu/l) | 7.45 ± 0.08 | 15.72 ± 0.40 | 19.91 ± 0.40 |
| ALP (iu/l) | 60.16 ± 0.69 | 67.41 ± 0.82 | 74.62 ± 1.01 |
| GGT (iu/l) | 19.67 ± 0.27 | 21.77 ± 0.35 | 22.47 ± 0.35 |

Statistical significance: $P < 0.05$.

**Table 2.** Comparison between the Parameters in Low, Moderate and High Parasite Densities

| Parameters | 1+ vs 2+ (P-value) | 1+vs 3+ (P-value) | 2+ vs 3+ (P-value) |
|---|---|---|---|
| ALT(iu/l) | <0.05 | <0.05 | < 0.05 |
| ALP (iu/l) | <0.05 | <0.05 | < 0.05 |
| GGT(iu/l) | <0.05 | <0.05 | > 0.05 |

1+ denotes low parasite density (1-10 parasites/100 thick film fields)
2+ denotes moderate parasite density (11-100 parasites/100 thick film fields)
3+ denotes high parasite density (1-10 parasites/ thick film field)

## RESULT

Table 1 above is based on the Mean Parasite Density per microlitre of blood and the corresponding liver function parameters. It was observed that parasite count of <1000 per microlitre of blood had alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) when compared with the parasite count of >1000 ≤ 9999 per microlitre of blood and >10000 per microlitre of blood. Parasite count of >1000 ≤ 9999 per microlitre of blood had lower values of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) when compared with the parasite count of >10000 per microlitre of blood.

## DISCUSSION

This study evaluated the effect of parasite density of *plasmodium* on the liver enzymes such as alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT). It has been reported that alkaline phosphatase activity in *falciparum* infected adult males and females were significantly higher than that of the control (healthy males) (Iwalokun *et al*., 2006). A significant increase was found in the serum activity of alkaline phosphatase in infected adult females. However serum alkaline phosphatase activity was also reported to be lower in infected males compared with their female counterparts (Ibrahim and Ubom, 2005).

The mean serum ALT activity was also reported to increase significantly in adult *falciparum* malaria patients when compared with healthy controls. Similarly, significant elevation in ALT activity was related to the degree of parasitaemia in the malarial children (Iwalokun *et al*., 2006). ALT is completely localized in the cytoplasm and with minimal damage or destruction of the liver cells, it easily passes into the plasma.

It was observed from the findings of this study that parasite count of <1000 per microlitre of blood had lower values of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) when compared with the parasite count of >1000 ≤ 9999 per microlitre of blood and >10000 per microlitre of blood. Parasite count of >1000 ≤ 9999 per microlitre of blood had lower values of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) when compared with the parasite count of >10000 per microlitre of blood. The result indicates that the higher the parasite density from <1000 per microliter of blood to >1000 ≤ 9999 per microliter of blood and > 10000 per microliter of blood the higher the levels of the liver enzymes such as the ALT, ALP and GGT easier when discussing- <1000 per microliter to name group 1, (>1000 ≤ 9999 per microliter) to be group 2, above >10000 per microliter - group 3

This finding of this study is in agreement with a study carried out in India by Satpathy*et al*., (2004) and in Afghanistan by Arsala *et al.* (2003). This increase is connected with the fact that part of the life cycle of the *Plasmodium falciparum* took place in the hepatocytes which brings about their pathological destruction and the spike in the enzyme levels.

For serum ALP, the mean was also higher as the parasite density increases. This increase in serum level of ALP in parasitaemic groups might be as a result of transient partial obstruction of the hepato-biliary tracts from inflammatory oedema of the hepatocytes, which is in agreement with a study carried out in Nigeria by Iwalokun *et al*., (2006). Another study carried out on Nigerian children and adolescents by Afonja, (1983) showedan

upper limit value of 31 KA units per deciliter in children between birth and twenty years of age. Another study also done in Nigeria by Edozien, (1965) had an upper limit of ALP for children between 5 and 15 years of age.

The post hoc analysis of the liver enzyme and severity of plasmodium parasitaemia showed a significant difference in ALT, ALP and GGT values at $p<0.05$ when the low group (1+) was compared with the moderate group (2+). This indicates that as the parasite density increases the levels of ALT, ALP and GGT also increases. Result also showed a significant difference in ALT, ALP and GGT values at $p<0.05$ when the low group (1+) was compared with the high group (3+) indicating that the higher the parasite density, the higher the levels of the liver enzymes. There was also a significant difference in the level of ALT and ALP at $p<0.05$ when the moderate group (2+) was compared with the high group (3+) indicating that the higher the parasite density, the higher the levels of ALT, and ALP. In view of the fact that ALP is essentially used in the diagnosis of cholestatic liver diseases (Martins, 2006), then it means that there was hepato-biliary obstruction as the the degree of parasitaemia increases. but there was however no significant difference in the GGT value when the moderate Group (2+) was compared with the high group (3+) at $p < 0.05$ significance.

This indicates no effect in the GGT value as the parasite density increases from the moderate to the high. This however contradicts the study by Iwalokun *et al*., (2006). GGT is a microsomal enzyme located at the biliary pole of liver cells. An increase in its values is associated with intrahepatic and extrahepatic cholestasis.

When ALT level increases it indicates that there is a disease of the liver. However, a normal ALT level does not necessarily mean that the liver is definitely normal. ALT is more elevated than AST in varying cases of necrotic inflammatory of the liver, showing its greater efficiency as a liver disease marker (Rosenthal and Haight, 1989). ASAT is an enzyme localized not only in the cytoplasm but also in the mitochondria and indicates more severe liver cell damage with necrosis. It is present in many tissues (muscle, myocardium, etc.), so ALT is more specific for the liver.

An increased level of GGT and ALP suggests that there may be possible blockage of the bile ducts, or injury to, or inflammation of, the bile ducts. This condition is known as cholestasis and it is characterized by an impairment, or failure, of bile flow and this injury to the liver is known as cholestatic liver injury, while the disease is known as cholestatic liver disease. When there is bile duct blockage or injury within the liver, the condition is known as Intrahepatic. Intrahepatic cholestasis sometime occur in people with primary biliary cirrhosis or liver cancer, for example. When there is a blockage of the bile duct or injury that occurs outside the liver, it is known as Extrahepatic cholestasis. This usually occurs in people with gallstones. When a blockage or inflammation of the bile ducts occurs, the GGT and ALP can overflow like a backed up sewer and seep out of the liver and into the bloodstream. These enzymes become markedly increased approximately ten times the upper limit of their normal values.(Rosenthal and Haight, 1989).

## CONCLUSION

The result from this study has shown that high plasmodium parasite density could result in liver injury. The degree of the hepatic injury may increase with increase in parasitaemia.

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