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**Malaria Surveillance in Schizophrenia Patients and its Effects on Hepatic and Red Cell Indices**ATERE Adedeji D.<sup>1,2\*</sup>, OKPOKO Favour I.<sup>2</sup>, ADEBAYO Teslim O.<sup>2,3</sup>, KOSAMAT Yekeen A.<sup>1</sup>, IGE Ilesanmi P.<sup>2</sup>

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**Abstract**

Schizophrenia is a complex illness with genetic, environmental, and epigenetic components, and malaria is a leading cause of illness, disability, and death in tropical countries. Complex relationships exist between malaria and mental problems. Malaria, a debilitating physical ailment, may lead to depression, which affects immunity and behaviour. The aim of this study is to investigate the effect of malarial on the hepatic and red cell indices of parasitized schizophrenics. This study recruited a sample of forty (40) individuals diagnosed with schizophrenia and malaria parasites, together with 30 controls who were matched in terms of age and gender. Six millilitres (6ml) of venous blood were drawn from each participant and dispensed appropriately. Level of C-reactive protein, liver function parameters [AST, ALT, ALP, Total Bilirubin (TBil), Conjugated Bilirubin (ConjBil), Total protein (TPro), and Albumin (ALB)], Red cell indices and malaria parasites were determined by standard laboratory techniques. Statistical analysis of data was done appropriately and p-values less than 0.05 was considered significant. Schizophrenic malaria patients had considerably lower PCV, RBC, and HGB than controls ( $p < 0.05$ ). TBil, ConjBil, and CRP were significantly greater in schizophrenic malaria patients than controls ( $p < 0.05$ ), but TPro and ALB were lower. PCV correlated positively with TBil, ConjBil, AST, and ALT ( $p < 0.05$ ). RBC had significant positive correlation with AST and ALT ( $p < 0.05$ ). Also, HGB showed positive significant correlation with ConjBil, AST and ALT ( $p < 0.05$ ). In this study, malarial parasite-infected schizophrenics

have considerable changes in hepatic and red cell indices. Malaria is associated with reduced red cell indices and heightened liver enzymes. This may be due to the parasites' increased red blood cell destruction.

**Keynote:** Schizophrenia, *Plasmodium falciparum*, anaemia, prevalence, red cell indices

**Introduction**

In tropical regions, malaria is an important factor contributing to poor health, neurological disability, and premature mortality. According to the estimates provided by the World Health Organization in 2014, there were 198 million clinical cases in 2013, which resulted in 584,000 fatalities (WHO, 2014). Severe malarial anaemia accounted for about three-quarters of all cases of malaria morbidity and 9% of all admissions in a typical paediatric emergency ward. The mortality rates were highest in sub-Saharan Africa, and 85–90% of the malaria-related deaths occurred among children under the age of five and pregnant women (Adebola and Olugbemiro, 2011; WHO, 2014; Atere *et al.*, 2020).

*Plasmodium falciparum* causes the majority of malaria-related deaths since it is the most common cause of severe and complicated malaria infections (Frimpong *et al.*, 2018; Zekar and Sharman, 2023). Parasitemia can express itself in a variety of ways, from asymptomatic parasitemia to a life-threatening illness. Coma, generalized convulsions, hyper parasitaemia, anaemia, fluid and electrolyte imbalance that can lead to acid-base disturbances, renal failure, hypoglycaemia, hyperpyrexia, cerebral malaria,

haemoglobinuria, circulatory collapse and shock, spontaneous bleeding, disseminated intravascular coagulation (DIC), pulmonary edema, and death can result from untreated *P. falciparum* infection (Becker and Kilian, 2006; Frimpong *et al.*, 2018). The long-term neurologic and cognitive abnormalities experienced by 25% of cerebral malaria survivors have become more widely recognized during the past 15 years (John *et al.*, 2008; Aaby *et al.*, 2020).

According to Huang and Liu (2017), schizophrenia is a widespread, severe mental illness that is typically characterized by abnormal perceptions, thoughts, emotions, volition, and behavior. It is a complicated syndrome with a wide range of symptoms. Positive, negative, and cognitive symptoms of schizophrenia can be categorized, however they are by no means mutually exclusive. Positive symptoms include unusual thoughts and behaviors, such as recurrent psychosis, which is characterized by delusions, hallucinations, and disordered speech and behavior. Recurrent psychosis is the 'loss of contact with reality'.

Complex relationships exist between malaria and mental problems. Malaria, a severe physical sickness, may predispose to depression, which affects immunity and behaviour (Racheal *et al.*, 2017). Research suggests that depression can slow recovery from malaria. *Plasmodium falciparum* infection can cause major morbidity and mortality in humans when it spreads to the liver (Parpen *et al.*, 2014; Racheal *et al.*, 2017). In the hepatic stage of malaria parasite's life cycle, the liver transforms sporozoites into merozoites and releases them into the bloodstream (Parpen *et al.*, 2014).

Schizophrenia has genetic, environmental, and epigenetic components, and malaria can cause neuro-disability and death in tropical regions (Akinlade *et al.*, 2014; Atere *et al.*, 2023). In the past 15 years, we have learned that 25% of people who survive cerebral malaria experience neurologic and cognitive abnormalities for the rest of their lives. In addition, recent studies have shown that malaria has an impact on liver parameters. The aim of the study was to

investigate the effect of malaria on liver and red cell indices in patients with schizophrenia presenting to Federal Teaching Hospital, Ido-Ekiti (FTHI), Ekiti State, Nigeria.

## Materials and Methods

### Study Design

The study is a comparative cross-sectional study conducted in a hospital setting, comparing individuals diagnosed with schizophrenia who are infected with *Plasmodium falciparum*, with patients who are apparently healthy and not infected with malaria. The study was carried out from January to August of 2020. This study recruited a sample of forty (40) individuals diagnosed with schizophrenia and malaria parasites, together with 30 controls who were matched in terms of age and gender. The participants were recruited from the psychiatric clinic of Federal Teaching Hospital, Ido-Ekiti (FTHI) after obtaining an informed consent from each participant and ethical approval from the Ethics Research Committee of the Federal Teaching Hospital, Ido-Ekiti (FTHI). The approval was granted under the registration number ERC/2018/04/04/116B. All the participants that took part in the study were between the ages of 18-65yrs. Patients with schizophrenia are evaluated medically using the Positive and Negative Syndrome Scale (PANSS) (Stefanović *et al.*, 2015). A qualified psychiatrist administered and documented each participant's PANSS score.

### Inclusion and Exclusion Criteria

**Inclusion Criteria (Cases and Control):** The study required participants to provide informed consent, satisfy the PANSS criteria for diagnosing schizophrenia, exhibit positive and negative scales within the range of 7 x 49 (Schizophrenia), and fall within the age range of 18 to 65. The control group consisted of individuals between the ages of 18 and 65 who had a PANSS scale score below 7, indicating the absence of schizophrenia.

**Exclusion Criteria (Case and Control):** The study excluded individuals who met the following criteria: being over the age of 65 (geriatric subjects), being under the age of 18, taking non-steroidal anti-inflammatory agents, steroids,

antidepressants, antipsychotic medications, or anti-convulsants within three weeks prior to presentation, having a previous history of mania or hypomania, experiencing concurrent psychotic symptoms, being pregnant, having serious and/or unstable medical disorders, Addison's disease, Cushing's disease, thyroid diseases, or being diabetic and hypertensive.

### Collection and Storage of Samples

Six millilitres (6ml) of venous blood were drawn each participant. For the Malaria test and Red cell indices, three (3ml) of venous blood was dispensed into an ethylene diamine acetate (EDTA) bottle and gently mixed by inverting the container several times. Three (3ml) of the obtained samples were dispensed into plain bottles and allowed to retract. Each sample was then spun for 5 minutes at 4000 rpm to extract serum, which was kept at -20°C until CRP and LFT values were estimated.

### Analytical Methods

A serum level of C-reactive protein was assayed using ELISA kits obtained from Melsin Medical Company, USA and liver function parameters (AST, ALT, ALP, TBil, ConjBil, Tpro and Alb) were determined by spectrophotometric methods (Abro *et al.*, 2009). Malaria testing was done using the CareStart™, Access Bio, Inc., USA in vitro rapid diagnostic kit based on antigens was carried out on aliquots of whole blood in duplicates as described by WPRO (2005), and Red cell indices were determined by haematological analyser.

### Statistical Analysis

A statistical package for social sciences version 25.0 (SPSS Inc, Chicago, IL) was used to

analyze the data. Analysis of variance (ANOVA) was used to compare schizophrenia with malaria, schizophrenia without malaria, and non-schizophrenic individuals without malaria. Correlation was applied to compare liver function and red cell indices in schizophrenia. Significant P values were 0.05 or less.

### Results

Table 1 shows the prevalence of *Plasmodium falciparum* infection among schizophrenic patients. *P. falciparum* positivity rate was higher in males (45.8%) than females (37.5%) in schizophrenia, and the overall prevalence rate of *P. falciparum* is 42.5%. Comparing the mean age and red cell absolute values among schizophrenic subjects with malaria, schizophrenic subjects without malaria and non-schizophrenic subjects without malaria using independent One-Way Analysis of Variance (ANOVA), the mean PCV, RBC and HGB were significantly lower in schizophrenic subjects with malaria than control (Table 2). In the same vein, the mean TBil, ConjBil and CRP were significantly higher in schizophrenic subjects with malaria than control group, while mean TPro and ALB were significantly lower. More so, TBil mean level was also significantly higher in schizophrenic subjects with malaria than those without malaria (table 3). Table 4 shows correlation between hepatic indices with severity of anaemia Indices (PCV, HGB and RBC) among schizophrenic subjects with malaria. PCV showed positive correlation with TBil, ConjBil, AST and ALT. RBC had significant positive correlation with AST and ALT. Also, HBG showed positive significant correlation with ConjBil, AST and ALT. In table 5, PCV had significant negative correlation only with TPro, but it showed direct significant correlation with TBil.

**Table 1: Prevalence of *Plasmodium falciparum* in Schizophrenia patients**

Gender	N	RDT	
		Positive (%)	Negative (%)
Male	24	11 (45.8)	13 (54.2)
Female	16	6 (37.5)	10 (62.5)
Total	40	17 (42.5)	23 (57.5)

RDT = Rapid diagnostic test kit

**Table 2: Mean age and Absolute Red Cell indices among schizophrenic subjects with malaria, schizophrenic subjects without malaria and non-schizophrenic subjects without malaria**

Parameters	Schizophrenic subjects with malaria (n=17)	Schizophrenic subjects without malaria (n=23)	Non-schizophrenic subjects (n=30)	P value
Age (Years)	42.91 ± 12.99	37.59 ± 11.00	38.33 ± 11.93	0.289
PCV (%)	37.50 ± 3.97 <sup>a</sup>	39.48 ± 4.08	40.89 ± 2.85 <sup>c</sup>	0.004
RBC (X10 <sup>12</sup> /L)	4.28 ± 0.56 <sup>a</sup>	4.52 ± 0.39	4.76 ± 0.49 <sup>c</sup>	0.004
HGB (g/dl)	12.53 ± 1.40 <sup>a</sup>	13.24 ± 1.28	13.49 ± 1.17 <sup>c</sup>	0.029
MCV (fl)	88.39 ± 6.46	88.12 ± 5.52	85.80 ± 4.87	0.192
MCH (pg)	29.17 ± 3.13	29.19 ± 2.21	28.46 ± 2.20	0.508
MCHC (g/dl)	32.80 ± 1.39	33.10 ± 0.93	33.00 ± 0.98	0.676

\*Significant at P = 0.05

a = significantly different from control, b = significantly different from Schizophrenic subjects with malaria group, c = significantly different from Schizophrenic subjects without malaria group

Key: PCV = Packed cell volume, RBC = Red blood cell, HGB = Haemoglobin concentration, MCV = Mean cell volume, MCH = Mean cell haemoglobin, MCHC = Mean cell haemoglobin concentration

**Table 3: Mean CRP and Hepatic indices among schizophrenic subjects with malaria, schizophrenic subjects without malaria and non-schizophrenic subjects without malaria**

Parameters	Schizophrenic subjects with malaria (n=17)	Schizophrenic subjects without malaria (n=23)	Non-schizophrenic subjects (n=30)	P value
TBil (mg/dl)	8.72 ± 3.34 <sup>a</sup>	7.57 ± 2.25 <sup>a</sup>	5.01 ± 2.05 <sup>b,c</sup>	0.000
Conj BIL(mg/dl)	3.10 ± 1.41 <sup>a</sup>	3.17 ± 1.33 <sup>a</sup>	2.32 ± 0.89 <sup>b,c</sup>	0.020
AST (U/L)	14.88 ± 9.37	16.65 ± 7.68	16.97 ± 6.08	0.643
ALT (U/L)	12.82 ± 5.76	13.57 ± 8.88	14.50 ± 6.39	0.733
ALP (U/L)	9.18 ± 4.61	9.83 ± 4.29	11.53 ± 3.67	0.129
TPRO (g/L)	60.92 ± 2.26 <sup>a</sup>	60.19 ± 2.60 <sup>a</sup>	63.24 ± 3.66 <sup>b,c</sup>	0.001
ALB (g/L)	32.37 ± 2.15	31.75 ± 2.80 <sup>a</sup>	33.60 ± 2.55 <sup>c</sup>	0.032
CRP (µg/ml)	1.30 ± 0.40 <sup>a</sup>	1.25 ± 0.27 <sup>a</sup>	1.07 ± 0.12 <sup>b,c</sup>	0.006

\*Significant at P = 0.05

a = significantly different from control, b = significantly different from Schizophrenic subjects with malaria group, c = significantly different from Schizophrenic subjects without malaria group

Key: TBil =Total bilirubin, ConjBil = Conjugated bilirubin, AST = Aspartate amino transferase, ALT = Alanine amino transferase,ALP=Alkaline phosphatase, TPRO=Total protein,ALB=Albumin, CRP=C-reactive protein.

**Table 4: Correlation between hepatic indices with anaemic indices (PCV, HGB and RBC) among schizophrenic subjects with malaria**

	PCV		RBC		HGB	
	r	p	r	p	r	p
TBil (mg/dl)	0.552	0.032*	0.284	0.269	0.458	0.065
Conj BIL (mg/dl)	0.660	0.004*	0.436	0.080	0.662	0.004*
AST (U/L)	0.646	0.005*	0.823	0.000*	0.706	0.002*
ALT (U/L)	0.514	0.035*	0.783	0.000*	0.582	0.014*
ALP (U/L)	0.060	0.820	0.082	0.755	0.142	0.586
TPRO (g/L)	-0.128	0.626	-0.264	0.307	-0.102	0.697
ALB (g/L)	-0.132	0.614	-0.214	0.409	-0.093	0.722
CRP (µg/ml)	0.136	0.602	0.444	0.074	0.226	0.384

\* Correlation is significant at the 0.05 level (2-tailed)



**Table 5: Correlation between hepatic indices with anaemic indices (PCV, HGB and RBC) among schizophrenic subjects without malaria**

	PCV		RBC		HGB	
	r	p	r	p	r	p
<b>TBil (mg/dl)</b>	0.455	0.029*	0.334	0.119	0.301	0.162
<b>Conj BIL (mg/dl)</b>	0.366	0.086	0.333	0.120	0.293	0.175
<b>AST (U/L)</b>	0.173	0.430	0.055	0.803	-0.016	0.941
<b>ALT (U/L)</b>	0.336	0.117	0.269	0.215	0.372	0.081
<b>ALP (U/L)</b>	0.284	0.189	0.292	0.176	0.337	0.116
<b>TPRO (g/L)</b>	-0.432	0.039*	-0.248	0.253	-0.314	0.144
<b>ALB (g/L)</b>	-0.124	0.572	-0.303	0.160	-0.021	0.926
<b>CRP (µg/ml)</b>	-0.130	0.555	-0.195	0.372	-0.144	0.511

\* Correlation is significant at the 0.05 level (2-tailed)

### Discussion

Several studies have been conducted on malaria as an infectious disease, which presents numerous health challenges. However, there is a scarcity of research specifically addressing the current topic. In the context of schizophrenia, the prevalence rate of *P. falciparum* was found to be greater in males (45.8%) compared to females (37.5%). The overall prevalence rate of *P. falciparum* was determined to be 42.5%. The study revealed a significant frequency of malaria. There are other elements that can be ascribed to this phenomenon, encompassing heightened mosquito attraction and physiological adaptations necessary for survival, as well as the environmental conditions within the health institution in question (WHO, 2015). The present discovery aligns with recent studies conducted by Yakubu *et al.* (2018) and Ikegbunam *et al.* (2022), which have reported elevated rates of malaria prevalence among pregnant women attending antenatal care units in various states of Nigeria. Additionally, Jenkins *et al.* (2019) have identified immunity as a significant risk factor for both malaria and mental disorders within the adult household population residing in rural Kenya.

Haematological abnormalities are considered a hallmark of malaria and are reported to be most pronounced in *P. falciparum* infections (Plewes *et al.*, 2019; Sakzabre *et al.*, 2020). Kotepui *et al.* (2015) showed that *P. falciparum* malaria infections can lead to significant changes of various blood cell parameters compared to

infections with *P. vivax*, including higher neutrophil and lower eosinophil responses.

The mean red cell absolute values of schizophrenic subjects with malaria, without malaria, and non-schizophrenic subjects without malaria were compared in this study. The mean PCV, RBC and HGB were significantly lower in schizophrenic subjects with malaria than control. This finding is consistent with previous research on malaria patients, which found that low haemoglobin concentration was one of the most important predictors of malaria infection (Maina *et al.*, 2010). Malaria and anaemia have complicated causes and effects. Infected RBCs have decreased deformability and changed surface features, which would normally cause them to be filtered and removed by the spleen. Infected and uninfected erythrocytes cluster together and clog the capillary and postcapillary venules of numerous organs, a process known as sequestration and rosetting. Malaria-related anaemia is exacerbated by increased breakdown of uninfected erythrocytes as well as a decrease in erythrocyte synthesis (Suwanarusk *et al.*, 2004; Saravu *et al.*, 2011). According to national guidelines for diagnosis and treatment, lower haemoglobin in malaria may be linked to accelerated breakdown of red blood cells by the parasites (Goselle *et al.*, 2009).

Meanwhile, mean total bilirubin (TBil), conjugated bilirubin (ConjBil), and C- Reactive Protein (CRP) levels in schizophrenic subjects with malaria were considerably higher than in

the control group, whereas mean TPro and ALB levels were significantly lower. Furthermore, the mean TBil level in schizophrenic participants with malaria was considerably greater than in those without malaria. While studying malaria patients, Deepti and Khushbu (2017) discovered substantial increases in the mean activity enzyme values of AST, ALT, ALP, and serum total and direct bilirubin. Infection of liver cells by the malarial parasite's sporozoite form can result in organ congestion, sinusoidal obstruction, and cellular inflammation. These changes in hepatocytes can lead to the leakage of parenchymal (transaminases) and membranous (alkaline phosphatase) enzymes of the liver into the circulation, resulting in an increase in liver enzymes and ALP observed in malaria infected patients (Onyesom, 2012). This shift could show that the hepatic stage of the parasite's life cycle in human hosts is accompanied by considerable disruption in hepatocytes parenchyma and membrane, resulting in liver enzyme leakage into the general circulation.

Packed cell volume (PCV) had a significant positive association with TBil, ConjBil, AST and ALT, red blood cell (RBC) had a significant positive correlation with AST and ALT, and haemoglobin (HBG) had a significant positive correlation with TBil, ConjBil, AST and ALT. These may be indicative of an earlier assertion that supported the causes for substantial red blood cell destruction in malaria patients. According to Ignatius *et al.* (2008), when malarial parasite density increased, so did liver enzyme leakage and bilirubin levels. Raised bilirubin in mild malaria is usually caused by haemolysis of parasitized and non-parasitized RBC and/or hepatocyte injury (Abro *et al.*, 2009).

This research may not be without limitations. The main limitation of this study is a confounding factor that may alter haematological parameters such as viral, bacterial, and helminthic infections in the studied population, as well as nutritional deficiencies and patients' genetic backgrounds, particularly among those living in developing countries.

### Conclusion

According to the findings of this study, the prevalence of malaria among schizophrenia is

considerably high, and schizophrenic individuals infected with malarial parasites have significant modifications and differences in a variety of hepatic and red cell indices. The lowered and elevated red cell indices and various liver enzymes in malaria may thus be related to the parasites' enhanced destruction of red blood cells. Malaria control policies should be promoted among schizophrenia patients since malaria can predispose to depression by affecting hepatic, red cell indices and modifying the behaviour of sick persons.

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### Authors' contributions

This work was carried out in collaboration between all authors. Authors ADA and OFI designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors ATP, KYA and OFI managed the analyses of the study. Authors ADA and OFI managed the literature searches. All authors read and approved the final manuscript.

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