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Assessment of Oxidative Protein Modification and Endothelial Markers in Malaria Infested Patients in Southern Nigeria

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Abstract: The precise pathways by which malaria infections contribute to increased blood pressure and organ impairment are not fully elucidated. This study sought to investigate the relationship between malaria infections and the extent of oxidative protein modification, along with changes in endothelial markers in the affected population. The research involved 330 participants, comprising 200 (60.6%) individuals diagnosed with malaria and 130 (39.4%) healthy controls. The presence of malaria parasites was confirmed through Giemsa-stained microscopy of thin blood films, while levels of ICAM-1, protein carbonyl groups, and SH groups were assessed using ELISA techniques. The findings indicated that both ICAM-1 and protein carbonyl levels were significantly elevated ($p<0.05$) in malaria-infected individuals compared to the control group, whereas SH group levels were significantly lower ($p<0.05$) in the infected subjects. Additionally, ICAM-1 and carbonyl levels were significantly lower ($p<0.05$) in male participants compared to females, while SH group levels were significantly higher ($p<0.05$) in males. No significant differences ($p>0.05$) were observed across all parameters concerning age. ICAM-1 exhibited a non-significant positive correlation with the carbonyl group ($r = 0.053$, $p = 0.765$) and a negative correlation with the SH group ($r = -0.251$, $p = 0.0146$). In contrast, the carbonyl group showed a significant negative correlation with the SH group ($r = -0.848$, $p = 0.000$). In summary, this study offers evidence of heightened endothelial activation and oxidative protein modifications in individuals with malaria parasitaemia.

Keywords: *Malaria, ICAM-1, Endothelial Activation, Oxidative Stress, Protein Modification.*

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I. INTRODUCTION

Malaria poses a serious threat to public health, particularly in endemic regions where approximately 3.3 billion individuals are at risk across 85 countries. This disease is predominantly found in tropical and subtropical climates, having been largely eradicated from temperate zones over the last century (Gomes et al., 2022). The transmission of malaria occurs through the bite of female Anopheles mosquitoes, and its prevalence is influenced by several factors, including altitude, climate, vegetation, and the effectiveness of control strategies. Additionally, socioeconomic factors such as poverty, natural disasters, and conflict significantly contribute to the disease's spread. Although less frequently, malaria can also be transmitted from mother to child or through blood transfusions, which poses a considerable risk in low-resource environments. The disease is caused by five species of parasites, with Plasmodium falciparum and Plasmodium vivax being the most dangerous (WHO, 2022). The global eradication of malaria is complicated by numerous challenges, including limited access to treatment, population movement to endemic areas, the absence of an effective vaccine, underdeveloped economies in affected regions, and, crucially, the emergence of resistance to antimalarial medications (Ashley et al., 2018).

Oxidative protein modification involves the chemical alterations that proteins undergo when exposed to reactive oxygen species (ROS) or oxidative stress. These changes can significantly impact the structure, function, and stability of proteins (Juan et al., 2021). A prevalent form of oxidative modification is the oxidation of specific amino acid residues, such as cysteine, methionine, and tryptophan, leading to the formation of disulfide bonds, sulfoxides, or carbonyl groups. Such modifications can change protein conformation, affect enzymatic activity, or disrupt protein-protein interactions. Other forms of oxidative modifications include protein nitration, glycation, and lipid peroxidation (Andrés et al.,

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2022). Modifications to proteins can result in dysfunction, aggregation, and a reduction in biological activity. Furthermore, oxidative modifications of proteins are associated with a range of diseases, including neurodegenerative conditions, cardiovascular issues, and cancer. To combat the adverse effects of oxidative protein modifications, cells utilize antioxidant defense systems, which include enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. These enzymes play a crucial role in reducing oxidative damage and preserving protein homeostasis (Singh et al., 2019).

Endothelial dysfunction is recognized as a significant contributor to the development of malaria. ICAM-1, a cell surface glycoprotein, is typically expressed at low levels in immune, endothelial, and epithelial cells but is up-regulated in response to inflammatory signals. Its primary function is associated with the transendothelial migration of leukocytes, where it governs leukocyte rolling, adhesive interactions with the vascular wall, and facilitates their passage through the endothelial barrier (Amersfoort et al., 2022). Moreover, ICAM-1 has been identified as having additional roles in the resolution of epithelial injury, as well as in both innate and adaptive immune responses during inflammation and tumor development. It is regarded as a vital regulator of various tissue functions throughout the initiation and resolution of pathological states. Despite ICAM-1 being a focus of clinical and therapeutic research, efforts to inhibit its activity have not resulted in notable improvements in the resolution of injuries (Blankson et al., 2022).

Malaria remains a significant public health challenge, impacting hundreds of thousands in Nigeria. The disease's pathogenesis is intricate, involving various factors such as oxidative stress and endothelial dysfunction. Although effective treatments are available, the rates of morbidity and mortality linked to malaria remain alarmingly high, underscoring the necessity for a deeper understanding of the mechanisms involved (Wu et al., 2011). While oxidative protein modification and endothelial markers have been associated with the pathogenesis of multiple diseases, their specific role in malaria-related endothelial dysfunction is not well understood. Consequently, this study seeks to evaluate the levels of oxidative protein modification and endothelial markers in patients suffering from malaria, aiming to explore their potential as biomarkers for assessing disease severity and progression.

II. METHODOLOGY

- *Study Area*

This research was conducted in General Hospitals located in Ekiti State, Nigeria.

- *Study Design*

A case-control research design was utilized for this study.

- *Ethical Approval*

Ethical clearance was obtained from the Ethics Committee of the College of Medicine and Health Sciences at Afe Babalola University, Ado Ekiti, Nigeria. Informed consent was secured from all participants prior to the initiation of the study.

- *Sample Size Determination*

The sample size (N) was determined using Fisher's formula (Safranek, 2018):

$n = z^2p(1-p) / d^2$

Where:

N = sample size

P = prevalence of malaria at 15.4% (WHO, 2022)

d = margin of error = 0.05

Z = confidence interval at 95%

Calculating this gives:

N = 1.962 * 0.154 (1-0.154) / 0.0025 = 200

Consequently, a total of three hundred and thirty (330) participants were enrolled in the study, consisting of 200 individuals with malaria as the subjects and 130 healthy, malaria-free individuals as the control group.

- *Inclusion and Exclusion Criteria*

Participants included in this study were malaria-infected patients aged between 18 and 50 years attending General Hospitals in Ekiti State. Those excluded were individuals not infected with malaria and those outside the age range of 18 to 50 years.

- *Sample Collection and Analysis*

Blood samples were collected in both SST and EDTA tubes and promptly sent to the laboratory for analysis. The presence of malaria parasites was assessed using Giemsa-stained microscopy of thin blood films, while ICAM-1, protein carbonyl groups, and SH groups were measured using the Enzyme Linked Immunosorbent Assay (Elabscience Inc.) following the manufacturer's guidelines.

- *Data Analysis*

Data from all participants and the outcomes of the conducted tests were recorded in Microsoft Office Excel 2007, and the analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 25.0. The significance of differences was evaluated through Analysis of Variance (ANOVA). Group comparisons were executed using Student's t-test, and correlation analyses were conducted using the Pearson test. A p-value of less than 0.05 was deemed statistically significant at a 95% confidence level.

III. RESULTS

Figure 1 illustrates the distribution of subjects and control participants. A total of 330 individuals were included

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in the study, consisting of 200 (60.6%) malaria-positive subjects and 130 (39.4%) apparently healthy control subjects. Figure 2 depicts the gender distribution among the subjects. Of the 200 subjects, 80 (40.0%) were male, while 120 (60.0%) were female. Figure 3 presents the age group distribution of the subjects. Among the 200 subjects, 111 (55.5%) were in the 18–25 years age group, and 89 (44.5%) were in the 26–50 years age group.

Table 1 displays the mean values of ICAM-1, carbonyl, and SH groups for both subjects and controls. The findings indicated that ICAM-1 and protein carbonyl levels were significantly elevated ($p<0.05$) in malaria-infected subjects compared to the control group, whereas the SH group was significantly ($p<0.05$) reduced in subjects relative to the control group. Table 2 outlines the mean values of ICAM-1, carbonyl, and SH groups concerning gender. The results revealed that ICAM-1 and carbonyl levels were significantly lower ($p<0.05$) in male subjects compared to female subjects, while the SH group was significantly ($p<0.05$) higher in male subjects than in female subjects.

Table 3 presents the average values of ICAM-1, Carbonyl, and SH groups categorized by age group. The findings indicate that both ICAM-1 and carbonyl levels were elevated in the 18 – 25 years age group compared to the 26 – 50 years age group, whereas the SH group levels were lower in the younger cohort. Nonetheless, no statistically significant differences ($p>0.05$) were observed across all parameters in relation to age. Table 4 illustrates the Pearson Correlation among ICAM-1, Carbonyl, and SH groups in the subjects. The analysis revealed a non-significant positive correlation between ICAM-1 and the carbonyl group ($r = 0.053$, $p = 0.765$), as well as a non-significant negative correlation with the SH group ($r = -0.251$, $p = 0.0146$). Conversely, a significant negative correlation was found between the carbonyl group and the SH group ($r = -0.848$, $p = 0.000$).

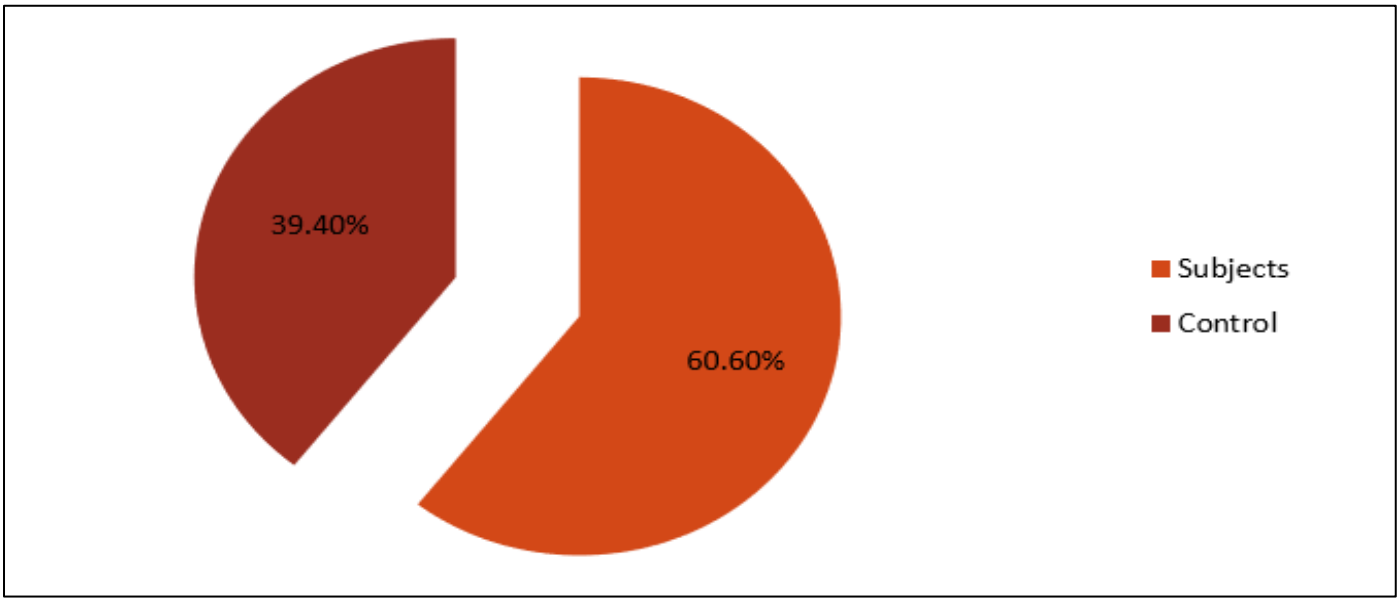

Fig 1 Distribution of Subjects and Control Participants

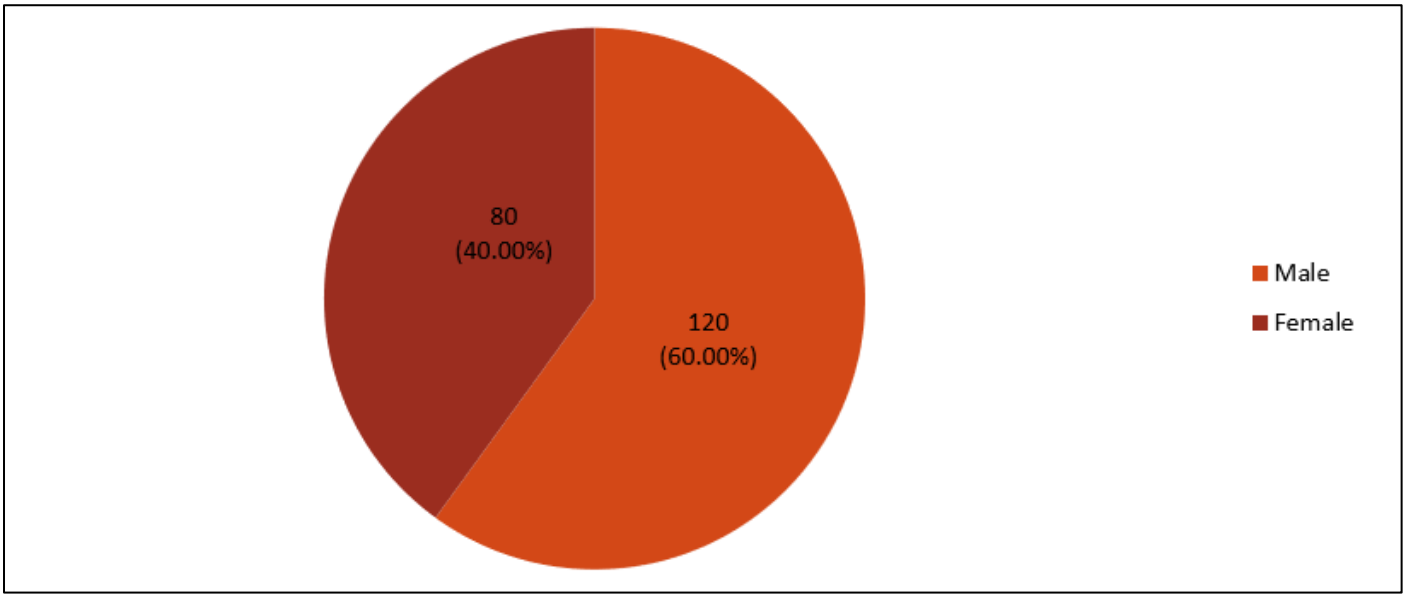

Fig 2 Distribution of Subjects according to Gender

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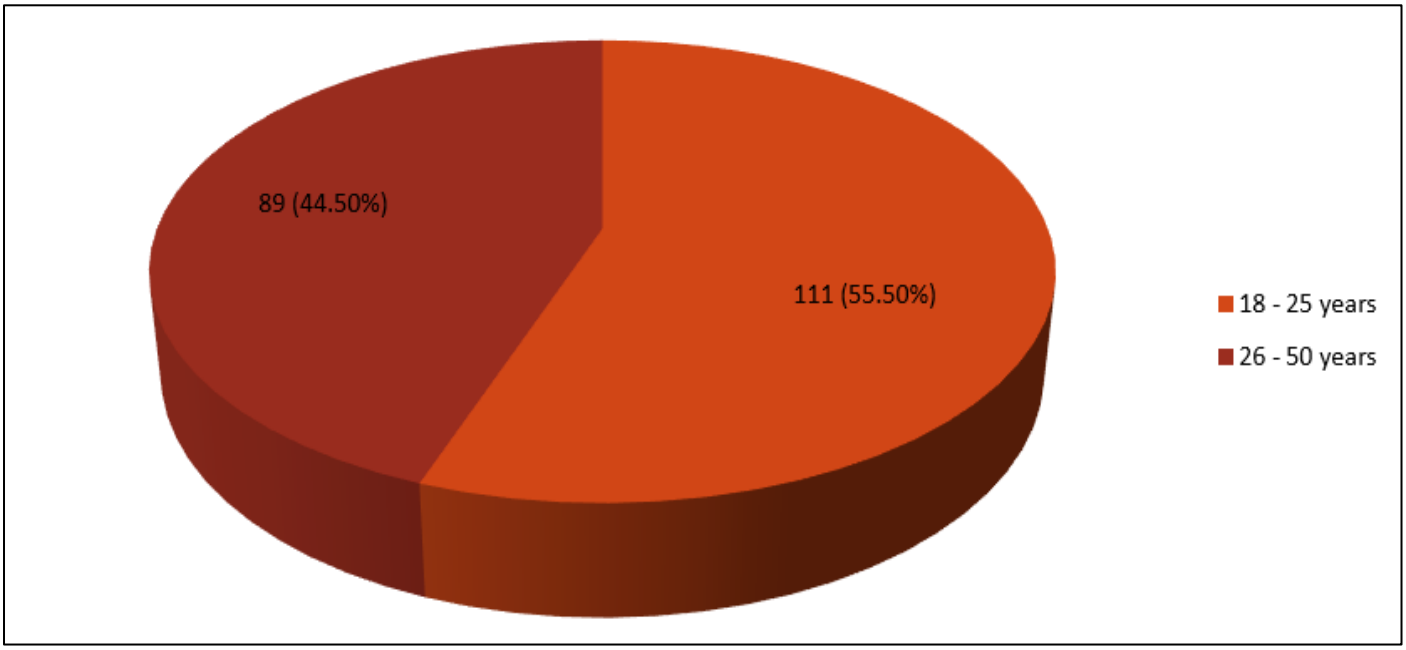

Fig 3 Distribution of Subjects according to age

Table 1 Mean values of ICAM-1, Carbonyl and SH Group in Subjects and Control

Parameters	**Subjects Mean ± SD (n = 200)**	**Control Mean ± SD (n = 130)**	**t-value**	**p-value**
ICAM-1 (ng/ml)	231.32±29.46	73.35±23.26	11.728	0.000
Protein Carbonyl (ng/ml)	82.43±4.75	65.37±5.49	8.313	0.001
SH group (µmol/l)	404.11±2.16	455.60±2.55	14.166	0.000

Keys: SH group: Protein sulfhydryl group; **ICAM-1**: Intercellular Adhesion Molecule-1

Table 2 Mean values of ICAM-1, Carbonyl and SH group in subjects with respect to gender

Parameters	**Male Mean ± SD (n = 120)**	**Female Mean ± SD (n = 80)**	**t-value**	**p-value**
ICAM 1 (ng/ml)	222.34±26.88	244.58±31.91	2.347	0.034
Protein Carbonyl (ng/ml)	78.11±2.17	85.28±3.27	6.605	0.000
SH group (µmol/l)	431.46±2.61	383.87±2.15	5.603	0.000

Keys: SH group: Protein sulfhydryl group; **ICAM-1**: Intercellular Adhesion Molecule-1

Table 3 Mean values of ICAM-1, Carbonyl and SH group in subjects according to age group

Parameters	**18 – 25 years Mean ± SD (n = 111)**	**26 – 50 years Mean ± SD (n = 89)**	**t-value**	**p-value**
ICAM 1 (ng/ml)	232.43±34.98	231.98±23.73	0.054	0.958
Protein Carbonyl (ng/ml)	83.41±4.81	81.80±4.62	1.142	0.270
SH group (µmol/l)	397.82±22.34	408.85±25.14	1.453	0.166

Keys: SH group: Protein sulfhydryl group; **ICAM-1**: Intercellular Adhesion Molecule-1

Table 4 Pearson Correlation of ICAM-1, Carbonyl and SH group in subjects

		ICAM-1	**Carbonyl group**	**SH group**
ICAM-1	Pearson Correlation		0.053	-0.251
	Sig. (2-tailed)		0.765	0.146
Carbonyl group	Pearson Correlation	0.053		-0.848**
	Sig. (2-tailed)	0.765		0.000
SH group	Pearson Correlation	-0.251	-0.848**	
	Sig. (2-tailed)	0.146	0.000	

**. Correlation is significant at the 0.01 level (2-tailed).

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IV. DISCUSSION

Malaria, particularly that is caused by Plasmodium falciparum, has been linked to an increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are thought to contribute to the progression of the disease and the emergence of complications (Nsonwu-Anyanwu et al., 2019). During a malarial infection, erythrocytes face oxidative stress from both intra- and extra-erythrocytic environments (Ertürk et al., 2020). The recent introduction of novel chemopreventive agents has highlighted the urgent need for biochemical markers, given the current absence of a suitable candidate biomarker for diagnosing malaria, assessing susceptibility, and evaluating chemopreventive efficacy (Gomes et al., 2022). It is essential to comprehend the critical factors that affect the clinical outcomes of infections for timely diagnosis and prevention. Consequently, this study aimed to explore the correlation between malaria infection and the degree of oxidative protein modification, as well as alterations in endothelial markers among the affected individuals.

Intercellular adhesion molecule-1 (ICAM-1) plays a crucial role as a cell adhesion molecule in the processes of inflammation and immune response. The upregulation of adhesion molecules like ICAM-1 during inflammation can contribute to tissue damage. ICAM-1 facilitates the migration of immune cells to inflamed areas, which in turn promotes the release of mediators such as chemokines and cytokines (Wiser, 2023). In this research, ICAM-1 levels were found to be significantly elevated in individuals with malaria compared to the control group. ICAM-1 is among several key cell adhesion molecules implicated in Plasmodium falciparum malaria. Both in vitro binding assays and field studies have demonstrated the importance of the cell-surface receptor ICAM-1 in the cytoadherence of P. falciparum (Mast et al., 2020). This aligns with findings from Mast et al. (2020) and Park et al. (2022), who reported heightened ICAM-1 levels in individuals with microscopic asymptomatic malaria. This suggests that endothelial cells may act as early responders to the presence of parasites in infected individuals, particularly when parasitemia is detectable by microscopy, in contrast to those with submicroscopic infections. However, a prior study noted elevated levels of endothelial activation molecules in a naïve population that developed submicroscopic infections during a controlled human malaria infection (Frimpong et al., 2021). The discrepancy between this previous research and our findings may suggest that individuals with natural infections develop some degree of tolerance to the parasite due to repeated exposure to Plasmodium, resulting in minimal upregulation of endothelial molecules at the subpatent level.

Protein carbonyls and protein nitrotyrosine serve as widely recognized and chemically stable indicators of protein oxidation. The protein carbonyls (PC) group arises from the direct oxidation of specific amino acid residues, notably lysine, arginine, threonine, proline, and histidine, or through secondary reactions with byproducts of lipid peroxidation (such as HNE) or glycoxidation involving lysine residues (Egwu et al., 2021). In this investigation, the levels of protein carbonyls were significantly elevated in individuals with malaria compared to control subjects. This observation aligns with earlier research that documented a notable increase in protein carbonyl levels among patients infected with malaria (Narsaria et al., 2020; Bilgin et al., 2021). The rise in protein carbonylation is likely due to a chronic elevation in reactive oxygen/nitrogen species, which can irreversibly interact with proteins to generate highly reactive carbonyl species, serving as precursors in the formation of advanced glycation end-products (AGEs) (Olaniyan et al., 2021). Compared to the oxidation of cysteine and methionine, carbonylated proteins are more challenging to induce, and heightened carbonylation levels, particularly in malaria cases, are believed to indicate not only oxidative stress but also protein dysfunction associated with the disease (Song et al., 2020). Consequently, carbonylated proteins can be utilized as biomarkers of oxidative stress due to their unique characteristics, including irreversibility, inability to be repaired, stability under various physical conditions, and their role in promoting protein aggregation, as proteins are essential biomolecules that facilitate cellular functions (Sachdev et al., 2021).

Thiol groups are sulfur-containing compounds found in proteins that possess antioxidant properties, primarily existing in plasma as they bind to albumin and amino acids. These thiols (-SH groups) can react with oxidants, leading to the formation of disulfide (RSSR) bonds, which represent their oxidized state (Ruiz et al., 2022). Disulfide bonds can subsequently be reduced back to thiol groups. Maintaining this balance is crucial for effective antioxidant defense and the regulation of apoptosis. An imbalance may lead to the generation of reactive oxygen species, resulting in endothelial dysfunction and apoptosis. Research indicates that plasma SH groups serve as significant extracellular scavengers of peroxides, providing protection to adjacent tissues (Checa & Aran, 2020). In our study, we observed a notable reduction in plasma -SH levels among malaria-positive individuals compared to the control group. This decline in SH levels suggests a potential impairment of plasma antioxidant defense mechanisms in malaria, aligning with findings from previous research (Sandikci et al., 2020; Kotepui et al., 2023). It remains unclear whether the reduction in –SH groups is a primary effect or a consequence of the disease process. The lower levels of –SH groups in patients compared to controls imply that these individuals may have experienced oxidative stress, which is known to contribute to endothelial dysfunction in malaria. Our results indicate that a deficiency in thiol/disulfide homeostasis could be implicated in the pathogenesis of malaria, as this balance is a fundamental factor in the disease process (Gomes et al., 2022). Conversely, chronic inflammation may be a significant contributor to the increase in oxidized thiol forms. Thus, the alterations in thiol/disulfide balance due to oxidative stress may be secondary to the disease process (Ertürk et al., 2020). However, given that this is a cross-sectional study, we cannot definitively determine whether these changes are primary or secondary to the disease.

In the present investigation, no notable differences were observed in the average values of ICAM-1, carbonyl group, and -SH group concerning age. Nevertheless, male

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participants exhibited significantly lower levels of ICAM-1 and carbonyl group ($p<0.05$) compared to their female counterparts, while the -SH group was significantly higher ($p<0.05$) in males than in females. This suggests that the severity of disease and its impact on the studied parameters were consistent across various age groups. However, as the disease progresses, individual patient circumstances may lead to different changes in some of these parameters (Narsaria et al., 2020). This is particularly evident in female subjects with malaria, who showed significantly ($p<0.05$) elevated levels of protein carbonyl group compared to male subjects.

In this research, ICAM-1 exhibited a non-significant positive correlation with the carbonyl group and a negative correlation with the -SH group. Conversely, a significant negative correlation was observed between the carbonyl group and the -SH group. It is well established that a robust antioxidant system can mitigate the excessive production of reactive oxygen species and oxidative stress. Consequently, it is not unexpected that malaria patients with reduced -SH group levels presented elevated values of ICAM-1 and the carbonyl group. The heightened levels of plasma ICAM-1 and carbonyl group indicate lipid peroxidation resulting from free radical release due to malaria parasites (Kayode et al., 2021). During the erythrocytic phase of the malaria parasite, essential amino acids derived from hemoglobin are crucial for the parasite's development and lifecycle continuation (Florens et al., 2022). Therefore, the presence of these parasites tends to promote the degradation of the host's hemoglobin, which serves as their nutritional source, facilitating their proliferation. The degree of hemoglobin degradation correlates with the severity of malaria (Nsiah et al., 2019). Thus, a decrease in hemoglobin levels is associated with increased oxidative stress, characterized by elevated levels of ICAM-1 and carbonyl groups, alongside a reduction in -SH group levels.

V. CONCLUSION

This study concludes that individuals with malaria parasitaemia exhibit heightened levels of endothelial activation and oxidative protein modifications. This finding indicates that endothelial activation may occur even in asymptomatic malaria infections, prior to the onset of clinical symptoms. Consequently, the increased expression of these molecules could be linked to damage inflicted by the parasite, likely through its sequestration to the host's endothelium, which may contribute to the constriction of blood vessels and the development of hypertension in malaria patients.

- *Declarations*

Ethics approval and consent to participate.

Ethical approval was obtained from the Ethics Committee at the College of Medicine and Health Sciences, Afe Bablola University, Ado Ekiti, Nigeria. Informed consent was secured from all participants prior to the initiation of the study.

- *Consent for publication*

Not applicable.

- *Availability of data and materials*

Data available from the corresponding author on reasonable request.

- *Competing interests*

None declared

- *Funding*

None

- *Author's Contributions*
- *All Auth*
- *Acknowledgements*

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