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# Evaluation of Some Haematological Biomarkers of Inflammation in Children with Varying Degrees of Malaria Parasitemia in a Tertiary Health Facility in Jos, Nigeria

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Authors MU and DOU designed the study, performed the statistical analysis, wrote the protocol, collected and analyzed sample collection, and wrote the first draft of the manuscript. Authors EKA managed the initial and final design of the study. Author EOT managed the analysis of the study. Author EDG managed the literature searches. Author YMG managed data and sample collection. All authors read and approved the final manuscript.*

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***Original Research Article***

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## ABSTRACT

**Aim:** This study aims to explore the correlation between specific haematological inflammatory markers and varying degrees of malaria in children, utilizing blood samples from children with malaria in Jos, Nigeria.

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**Study Design:** A cross-sectional study involving 384 clinically symptomatic and laboratory-confirmed malaria-infected children with diverse parasitemia levels. Samples were obtained from both outpatient and hospitalized cases at Jos University Teaching Hospital.
**Place and Duration of Study:** The study was conducted in Jos University Teaching Hospital. Data collection spanned a specified duration of 14th September 2022 to 14th may, 2023.
**Methodology:** Malaria parasite density was determined through microscopic examination of peripheral blood films. Complete blood counts were analyzed, and predictive inflammatory biomarkers were computed.
**Results:** Significant correlations among haematological inflammatory markers were evident, with the following sequence of significance observed: Neutrophil Lymphocyte Ratio displayed the most pronounced positive correlation with malaria parasite density (r=0.683, p=0.001), followed by Monocyte Lymphocyte Ratio (r=0.512, p=0.001), and Systemic immune Inflammatory Index (r=0.550, p=0.001). Eosinophil count exhibited marked significance, displaying a notably higher value in subjects with elevated malaria parasitemia compared to those exhibiting low, mild, and moderate levels (p=0.0154).
**Conclusion:** In conclusion, the investigation unveiled a robust relationship between malaria parasitemia and Haematological inflammatory markers, The prominence of NLR in exhibiting the strongest correlation with malaria parasite density underscores its potential as a vital biomarker for assessing malaria severity. They all offer cost-effective means to gauge malaria severity and assess inflammation in resource-limited settings. These markers also hold promise for malaria prognosis and treatment monitoring.

*Keywords: Biomarkers; malaria; correlation; prognosis.*

## 1. INTRODUCTION

Malaria, a significant global health concern triggered by Plasmodium parasites and transmitted through female Anopheles mosquitoes, it has continued to impose a considerable burden on human populations [1]. The World Health Organization (WHO) underscores that nearly 3.8 billion individuals spanning 91 countries, primarily in developing regions, are susceptible to malaria infection [2]. Despite substantial strides in curbing malaria's worldwide ramifications, WHO report for 2019 documented 229 million malaria cases and 409,000 associated fatalities, with 94% of these instances concentrated in Africa [2]. As the most severe global parasitic infection, approximately 40% of the global population remains vulnerable to contracting malaria [3].

Haematological biomarkers have surfaced as crucial indicators of immune responses and the severity of diseases linked to malaria parasitemia. Thrombocytopenia, characterized by a decreased platelet count, is commonly observed in malaria-infected individuals, rendering it a pivotal biomarker for assessing inflammation and disease intensity [4,5]. Platelets play a diverse role in immune responses, engaging in both inflammation and modulation of the immune system [6]. In the context of malaria, thrombocytopenia arises from various factors, such as platelet retention within the spleen, destruction due to immune responses, and utilization during coagulation processes [6]. The significance of this biomarker stems from its correlation with unfavorable clinical outcomes, including the development of severe illness and heightened mortality rates [6]. Monitoring platelet counts offers clinicians valuable insights into disease progression and the efficacy of therapeutic interventions. Alterations in leukocyte counts, encompassing monocytes, lymphocytes, and neutrophils, provide insightful perspectives into the immune response during malaria infection [7,8,9]. The ratios of monocytes to lymphocytes and neutrophils to lymphocytes exhibit potential as indicators of both inflammation and disease severity in malaria [10,11]. Research has indicated that there is an elevation in eosinophil counts in reaction to Plasmodium infection [12]. This increase in eosinophil concentration implies an intrinsic inflammatory mechanism, underscoring the active engagement of eosinophils within the immune response directed against the parasite.

Haematological biomarkers hold valuable potential for assessing risk and monitoring malaria patients. Integrating haematological analyses into routine clinical practices, alongside existing diagnostic tools, can facilitate early detection, personalized treatment strategies, and

effective malaria management. However, acknowledging the complexities of these biomarkers is crucial, considering the variations in haematological responses across diverse Plasmodium species and host populations, necessitating further exploration. Furthermore, obtaining a comprehensive understanding of the precise mechanisms underpinning these haematological changes and their implications in disease pathogenesis demands thorough investigation. Future research endeavors should focus on standardizing the application of haematological biomarkers in clinical settings, unveiling their prognostic and predictive capabilities for malaria. Addressing these dimensions will contribute to advancing our comprehension of malaria's underlying pathogenesis, elevating patient care quality, and enhancing outcomes in regions profoundly affected by the disease.

## 2. METHODOLOGY

### 2.1 Study Design and Participants

The study employed a cross-sectional research design to investigate the relationship between haematological inflammatory markers and malaria parasitemia in children. The study was conducted at the Jos University Teaching Hospital, Plateau State, Nigeria, from 14th September 2022 to 14th May 2023. The target participants were malaria-infected children aged zero (0) to seventeen (17) years. The study included 384 participants who presented with clinical symptoms and had laboratory-confirmed malaria infection. Children with tumors, cardiovascular conditions, and adults above seventeen (17) years were excluded from the study.

### 2.2 Sample Size Calculation and Sampling

The sample size of 384 participants was determined based on a calculated sample size to achieve adequate statistical significance. The systematic sampling technique was used to recruit participants from the hospital's outpatient department and hospitalized patients. This technique ensures that every 3rd participant was included, enhancing representativeness.

### 2.3 Data Collection Instruments

Venous blood samples were collected from each participant to assess haematological markers. The microscopic method was employed to determine malaria parasite density as thus; the film was examined microscopically with ×100 objective lens, with a total of 200 fields examined microscopically for each film, positive findings were graded on the thin smear using the ‘plus’ system scale. These scores were used to estimate parasite densities: + = 10 to 90 parasites/µl; ++ = 100 to 1,000 parasites/ µl, +++ = 1,000 to 10,000 parasites/µl; ++++ = > 10,000 parasites/µl, they were graded as thus; +=low, ++= mild, +++=moderate, and ++++=high. Predictive inflammatory biomarkers, namely Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Systemic Immune-Inflammation Index (SII), were calculated from complete blood count results.

- NLR: Neutrophil count / Lymphocyte count
- MLR: Monocyte count / Lymphocyte count
- SII: Neutrophil count × Platelet count / Lymphocyte count [13]

The complete blood count data were used to calculate these ratios, which are established indicators of inflammation.

### 2.4 Procedures

Participants were recruited from the outpatient department and hospitalized patients. Venous blood samples were collected from each participant, and microscopic examination was conducted to determine the malaria parasite density. The study took place within the Jos University Teaching Hospital setting.

### 2.5 Data Analysis and Presentation

Statistical analyses were performed using the IBM SPSS Statistics 28. Descriptive statistics, including simple percentages and mean ± standard deviation, were used to summarize the data, Pearson's correlation coefficient was used to determine linear correlation between the levels of certain hematological markers and the degree of malaria parasitemia, and T-Test was used to test significant associations. These measures facilitated the presentation of both individual markers and their relationship with malaria parasitemia.

### 2.6 Ethical Considerations

The study obtained ethical approval and informed consent from the Health Ethics and Research Committee of the University of Jos

Teaching Hospital. This ensured the protection of participants' rights and welfare.

## 2.7 Study Limitations

The study had several limitations, including:

- Lack of established reference ranges for inflammatory markers in the study area.
- Focus solely on children under eighteen (18) years of age, potentially limiting generalizability.
- Absence of evaluation of inflammatory markers in malaria co-infection.
- Lack of comparison with non-malaria-infested patients, which could provide valuable context.

## 3. RESULTS AND DISCUSSION

Malaria, a parasitic disease, triggers inflammation through intricate interactions involving the host, parasite, and environmental factors [14]. The response to malaria infection in humans entails diverse activities mediated by cell-intrinsic and systemic pathways, with initial non-specific responses in naive hosts [9]. Extensive research has been dedicated to identifying dependable predictors of malaria exposure, susceptibility, and severe complications. This study focuses on exploring the connection between specific surrogate inflammatory markers and children infected with Plasmodium falciparum.

(Table 1) portrays the socio-demographic characteristics of 384 children affected by malaria. Of this cohort, 43.5% (167) were female, while 56.5% (217) were male. The distribution across age groups demonstrated that 16.7% (64) were infants, 20.8% (80) were toddlers, 29.4% (113) were in the school-age bracket, and the majority, accounting for 33.1% (127), were adolescents. In terms of education, 46.9% (180) had not yet commenced schooling, 31% (119) were in primary education, 18.8% (72) were pursuing secondary education, and only 3.4% (13) were engaged in tertiary education. In the realm of religion, 53.1% (204) identified as Muslims, while 46.9% (180) ascribed to Christianity. Ethnic diversity revealed that 12% (46) belonged to the Berom group, 10.7% (41) were Fulani, 29.7% (114) were Hausas, 4.9% (18) represented Igbos, 8.1% (31) identified as Angas, and 5.5% (21) were Yoruba, with other minority ethnicities comprising about 29.4% (113). Geographical distribution unveiled that 45.3% (174) were urban residents, 35.9% (138) inhabited rural areas, and 18.8% (72) resided in suburban locales. The density of malaria parasites was categorized as low (10.7%, 41 cases), mild (67.7%, 260 cases), moderate (7.8%, 30 cases), and high (13.8%, 53 cases). The investigation demonstrated that socio-demographic factors, namely age (P=0.0012), educational level (P=0.043), ethnicity (P=0.001), and religion (P=0.015), significantly influenced parasitemia levels in malaria patients. Conversely, variables such as sex (p=0.856) and place of residence (0.493) did not exert a significant impact on parasitemia levels in subjects afflicted with malaria, all as shown in Table 1 . These findings underscore the intricate interplay between socio-demographic factors and the severity of parasitemia in children with malaria, underscoring the imperative of a comprehensive comprehension and targeted strategies in the management of this infectious disease.

The study found a significant increase in eosinophil count among subjects with high malaria parasitemia (P= 0.0154), aligning with prior research on acute Plasmodium falciparum infection [15], this suggests a cytotoxic role of eosinophils against parasitic infections, facilitated by T-helper cells and immune cytokines during the acute phase of malaria infection. While malaria parasitemia levels did not significantly impact the white blood cell count, there was a notable rise in eosinophil, neutrophil, and platelet counts, along with predictive inflammatory immune markers MLR, NLR, and SII (Table 2). These findings correspond to earlier reports on changes in white blood cell counts and inflammatory markers during acute Plasmodium falciparum infection [12]. It is important to note that haematological alterations like anemia, thrombocytopenia, and leukocyte count changes can occur due to malaria infection, although this study did not assess confounding factors such as hemoglobinopathies, nutritional status, and malaria immunity as done in previous works [12].

Furthermore, the study demonstrated a positive correlation between NLR and malaria parasite density (Table 3), consistent with previous reports on imported malaria patients [16]. Other studies also found higher NLR in severe falciparum malaria compared to uncomplicated cases [10,17]. NLR is suggested as a marker for stress and inflammation, indicating that higher malaria parasitemia induces greater stress and inflammation [10,17]. Similarly, the study established a strong positiv correlation between

**Table 1. Showing Demographic Data of Subjects**

| Characteristics | | Frequency (N) | Percentage (%) | P Value |
|---|---|---|---|---|
| **Age (years)** | Less than a year (infant) | 64 | 16.7 | 0.0012 |
| | 1-3 years (Toddler) | 80 | 20.8 | |
| | 4-9 years (School age) | 113 | 29.4 | |
| | 10-17 years (Adolescent) | 127 | 33.1 | |
| **Education** | Yet to start | 180 | 46.9 | 0.043 |
| | Primary | 119 | 31.0 | |
| | Secondary | 72 | 18.8 | |
| | Tertiary | 13 | 3.4 | |
| **Sex** | Female | 167 | 43.5 | 0.856 |
| | Male | 217 | 56.5 | |
| **Religion** | Christian | 180 | 46.9 | 0.015 |
| | Islam | 204 | 53.1 | |
| **Ethnicity** | Berom | 46 | 12.0 | 0.001 |
| | Fulani | 41 | 10.7 | |
| | Hausa | 114 | 29.7 | |
| | Igbo | 18 | 4.9 | |
| | Angas | 31 | 8.1 | |
| | Yoruba | 21 | 5.5 | |
| | Others | 113 | 29.4 | |
| | | | | 0.493 |
| **Residence** | Rural | 138 | 35.9 | |
| | Suburban | 72 | 18.8 | |
| | Urban | 174 | 45.3 | |
| **Parasite density grade** | Low | 41 | 10.7 | |
| | Mild | 260 | 67.7 | |
| | Moderate | 30 | 7.8 | |
| | High | 53 | 13.8 | |

**Table 2. Showing Association Between the Parasite Density Grading and Some Haematological Inflammatory Biomarkers**

| Variables | Low | Mild | Moderate | High | p-values |
|---|---|---|---|---|---|
| WBC ($10^3$/µL) | 8.1 ± 0.52 | 10.2 ± 0.57 | 8.9 ± 0.65 | 10.6 ± 1.58 | 0.426 |
| Neutrophil (%) | 43.5 ± 2.72 | 43.0 ± 1.18 | 52.0 ± 3.52 | 49.5 ± 2.54 | 0.016 |
| Lymphocyte (%) | 42.3 ± 2.80 | 43.6 ± 1.12 | 36.1 ± 3.09 | 37.9 ± 2.35 | 0.045 |
| Monocyte (%) | 11.5 ± 0.77 | 12.6 ± 0.40 | 11.3 ± 0.48 | 10.7 ± 0.30 | 0.129 |
| Eosinophil (%) | 3.70±0.11 | 3.16±0.22 | 3.26±0.21 | 3.74±0.42 | 0.0154 |
| Platelet ($10^3$/µL) | 280.4 ± 22.98 | 258.1 ± 9.00 | 165.7 ± 24.50 | 174.7 ± 20.61 | 0.001 |
| NLR | 1.6 ± 0.30 | 3.2 ± 0.70 | 2.2 ± 0.36 | 1.8 ± 0.19 | 0.001 |
| MLR | 0.43 ± 0.112 | 0.65 ± 0.142 | 0.36 ± 0.030 | 0.43 ± 0.109 | 0.001 |
| SII | 435.9 ± 74.87 | 849.9 ± 232.40 | 388.9 ± 133.27 | 246.3 ± 34.8 | 0.001 |
| Parasite density (p/µL) | 86.0 ± 2.05 | 417.1 ± 14.32 | 2426.3 ± 387.80 | 39837.8 ± 1939.85 | 0.001 |

**Table 3. Correlation of Immune-Inflammatory Markers of Malaria Patients to malaria parasite density**

| Immune-Inflammatory Markers | Correlation co-efficient (r) | P-value |
|---|---|---|
| Neutrophil/Lymphocyte Ratio | 0.683 | 0.001 |
| Monocyte/Lymphocyte Ratio | 0.512 | 0.001 |
| Systemic Inflammatory Index (SII) | 0.550 | 0.001 |

MLR and malaria parasite density, (Table 3), corroborating previous research [10,18,19] reported that increased MLR was associated with higher parasitemia in children up to five years old, suggesting MLR as a valuable indicator of malaria severity and the immune response's efficacy against the infection. Additionally, the study identified a significant positive correlation between SII and different grades of malaria parasitemia (Table 3), supporting previous studies on its potential prognostic value in various cancers [20] and malaria patients [21], Only a few studies have explored this innovative inflammatory marker in individuals with malaria, and our research adds to the existing literature on haematological inflammatory biomarkers.

Haematological biomarkers play a crucial role in evaluating inflammation and immune activation during malaria infection. Integrating haematological analyses into routine clinical practice can enhance the assessment of risk, early detection, and management of malaria. Further research should focus on standardizing these biomarkers and exploring their prognostic and predictive capabilities across diverse settings and populations.

## 4. CONCLUSION

The study demonstrated a positive correlation between different levels of malaria parasite density and most inflammatory immune markers, including MLR, NLR, and SII. Demographic factors such as age, ethnicity, educational level, and religion significantly influenced the levels of parasitemia among malaria patients, highlighting the importance of considering these factors when evaluating inflammatory biomarkers in specific populations. These findings also suggest that selected inflammatory biomarkers can serve as valuable tools in resource-limited areas to assess malaria severity and tailor appropriate interventions. Monitoring haematological biomarkers provides insights into the inflammatory response, immune cell activation, and haematological changes during malaria infection. However, to enhance disease assessment and treatment monitoring, it is crucial to consider combining multiple biomarkers for a comprehensive understanding of the inflammatory state during malaria infection.

## CONSENT

All authors unanimously declare that written informed consent was obtained from the participants for publication of this case study.

## ETHICAL APPROVAL

Ethical approval (ref; JUTH/DCS/IREG/127/XXXI/349) was obtained from Jos University Teaching Hospital Research and Ethics Committee before the commencement of the study.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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