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Evaluation of Bone Marrow Response in Different Degrees of Malaria Parasitemia in Children

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ABSTRACT: Malaria remains a significant public health concern, particularly in endemic regions, where it poses a severe risk to children and can lead to increased morbidity and mortality. Hence, the objective of this paper is to evaluate the haematological parameters and reticulocyte counts in children in fifty (50) children aged 5 to 12 years with various malaria parasitemia attending a tertiary teaching hospital at Elele, Rivers State, Nigeria using appropriate standard techniques. The study revealed a significant increase in mean reticulocyte counts in the test group (3.1 ± 1.12%) compared to the control group (2.0 ± 0.82%), indicating a robust bone marrow response to malaria infection. Results also provide evidence that malaria parasitemia is closely linked to changes in the TWBC and showed significant differences in other haematological parameters, with p-values < 0.05 for reticulocyte counts and other key metrics, suggesting a strong correlation between malaria parasitemia and bone marrow activity. The results of this study show how important the bone marrow is in fighting malaria infections in children. The big rise in reticulocyte counts shows how the body tries to cope with anaemia caused by malaria.

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Malaria remains one of the leading causes of morbidity and mortality in children, especially in sub-Saharan Africa, where the disease is common (Sarfo *et al.*, 2023). It happens when tiny parasites called *Plasmodium* get into the body. *Plasmodium falciparum* and *Plasmodium vivax* cause major human malaria, but *P. falciparum* is the more virulent, responsible for approximately a third of the

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deaths associated with the disease (Haldar and Mohandas, 2009a). Even though people and organizations around the world are trying to stop malaria, children remain disproportionately affected due to their developing immune systems. Malaria parasitemia is the presence of malaria parasites in the blood (Abossie *et al*., 2020; Tsegaye *et al.*, 2021). This condition can be mild or severe, and it affects how well the body can respond to the illness. One important part of this response is the bone marrow, which produces new blood cells to help the body fight back the infection (McKenzie *et al.,* 2005; Mohandas and An, 2012).Both *P. falciparum* and *Plasmodium vivax* induce anaemia during their blood stages of infection. Anaemia is a condition that results from a lack of red blood cells or dysfunctional red blood cells in the body. This leads to reduced oxygen flow to the body's organs (White, 2018). Malaria anaemia appears to be multifactorial. It involves increased removal of circulating erythrocytes as well as decreased production of erythrocytes in the bone marrow (Haldar and Mohandas, 2009). The bone marrow is a spongy tissue found within bones. It is responsible for producing blood cells, including red blood cells, white blood cells, and platelets. These reticulocytes are immature red blood cells released into the bloodstream by the bone marrow. They are critical components of red blood cell production and serve as indicators of the bone marrow's activity in response to blood loss or destruction, such as that caused by malaria (Boes and Durham, 2017). In malaria, the destruction of red blood cells leads to anaemia and requires increased production of reticulocytes (Mohandas and An, 2012). But how exactly does malaria parasitemia affect the bone marrow's ability to produce these reticulocytes? Does the severity of parasitemia correlate with a more pronounced bone marrow response? These are important questions that need to be answered, especially concerning children, who are more vulnerable to both malaria and anaemia. However, the molecular mechanisms of malarial anaemia are largely unknown (Chang and Stevenson, 2004; Haldar and Mohandas, 2009a).

Historically, malaria research has focused primarily on the direct effects of the parasite on red blood cells and the associated anaemia (Mawson, 2013; Paul and Brey, 2003; White, 2018). However, recent studies have argued the need to explore the indirect effects on the bone marrow's function. Understanding the reticulocyte count and its relationship with malaria parasitemia may provide new insights into the body's compensatory mechanisms and the overall severity of the disease (Antwi-Baffour *et al.,* 2023; Dumarchey *et al.,* 2022; Leong *et al.,* 2022; White, 2022). Malaria parasite ligands have been investigated for their remodelling of erythrocytes and their possible roles in the destruction of mature erythrocytes (Molina-Franky *et al.,* 2023; Moxon *et al.,* 2011). Polymorphisms in cytokines have been associated with susceptibility to severe malarial anaemia; these cytokines and malaria "toxins" likely function by perturbing erythropoiesis (Dumarchey *et al.,* 2022; Midha, 2017). The packed cell volume (PCV) is also a key indicator of anaemia and is commonly used to assess the degree of red blood cell destruction in malaria. Alongside PCV, Hb levels give an estimate of oxygen-carrying capacity, providing a comprehensive picture of a child's haematologic response to malaria (Onohuean *et al.,* 2023). Several co-infections increase susceptibility to malarial anaemia, likely because they exacerbate inflammation caused by malaria. Because of the complexities involved, the study of severe malarial anaemia may need a "systems approach" to yield a comprehensive understanding of defects in both erythropoiesis and immunity associated with the disease (Haldar and Mohandas, 2009a; Raiten *et al.,* 2015).

As the fight against malaria continues, could understanding the bone marrow response hold the key to improving treatment strategies for children? Even so, is there a correlation between malaria parasitemia and reticulocyte counts in children, and how do these factors influence other haematological parameters?

Plasmodium falciparum is a protozoan parasite that causes the most virulent form of human malaria and kills at least one million children annually. The asexual blood-stage parasite infects the mature red blood cell, and these stages of infection are responsible for all of the symptoms and pathologies associated with malaria (Zekar and Sharman, 2024). Mild malaria causes fevers and chills that come and go in cycles. This happens because of the life cycle of the parasites inside the red blood cells. Severe malaria, on the other hand, includes multiple additional pathologies, including lactic acidosis, cerebral malaria (resulting from the adhesion of infected erythrocytes with the endothelium in the brain) and severe anaemia (White, 2022). Of these pathologies, severe anaemia (defined as haemoglobin concentrations of $< 5\,\mathrm{g/dL}$ remains the least understood and also impacts significantly on vulnerable populations like children and pregnant women (Shi *et al.,* 2022; Stephen *et al.,* 2018).

As a result, malaria has drawn significant attention from researchers (Bakken and Iversen, 2021; Holding

and Kitsao-Wekulo, 2004; Jagannathan, 2018; Milner *et al.,* 2020). A growing body of literature has explored the haematological effects of malaria, with an increasing focus on how the body's bone marrow responds to the infection (Kotepui *et al.*, 2020; Naser *et al.,* 2024). The reticulocyte count, packed cell volume (PCV), and haemoglobin (Hb) levels have been frequently analyzed to understand the body's compensatory mechanisms in cases of malaria-induced anaemia (Onohuean *et al.,* 2023; Safeukui *et al.*, 2015). However, there are still gaps in understanding the precise relationship between varying degrees of malaria parasitemia and the bone marrow's capacity to respond through reticulocyte production.Early studies investigated the effects of severe malaria on reticulocyte counts in children. Kaboré *et al.,* (2020) Found that children with severe malaria had significantly lower reticulocyte counts compared to healthy controls. This was attributed to the destruction of red blood cells by the malaria parasite, leading to increased hemolysis and a compensatory decrease in reticulocyte production. Kotepui *et al*., (2015) Highlighted that malaria leads to the destruction of red blood cells, resulting in severe anaemia, especially in children under five. Their study primarily focused on quantifying red blood cell loss and analysing its direct correlation with malaria parasite density. However, while this research provided essential data on anaemia, it stopped short of investigating bone marrow function and its response to the infection. This limitation left unanswered the questions concerning how well the bone marrow compensates for this red blood cell loss. Without this understanding, it remains difficult to develop targeted interventions that address both red blood cell destruction and regeneration in children.

In another study, Pathak and Ghosh (2016) examined the reticulocyte count in children with moderate to severe malaria parasitemia. Their findings indicated a marked increase in reticulocyte counts in children with higher parasitemia levels, suggesting that the bone marrow becomes more active in response to more severe infections. However, the authors also noted that in cases of very high parasite densities, reticulocyte production was impaired. This raises a key point of contention: does the bone marrow reach a threshold beyond which it can no longer compensate for red blood cell destruction?

Antwi-Baffour *et al.* (2023) conducted a study exploring the relationship between reticulocyte counts and packed cell volume in pediatric malaria patients. Their work revealed a consistent inverse correlation between malaria parasitemia and PCV, reinforcing the notion that as parasite density increases, the destruction of red blood cells becomes more pronounced, leading to lower PCV levels. However, their study did not consider other factors that could influence the bone marrow's response, such as nutritional status or pre-existing health conditions. This omission leaves room for further investigation into how these factors may interact with malaria parasitemia to affect the bone marrow's output of reticulocytes.

There are, however, opposing results when we look at the connection between haemoglobin levels and reticulocyte counts in people with malaria. According to Kaboré et al. (2020), children with severe malaria often present with both low Hb levels and high reticulocyte counts. The researchers hypothesised that this reflects the bone marrow's attempt to compensate for haemoglobin loss by producing more reticulocytes. However, Quintero *et al.* (2011) found that in cases of chronic malaria infection, the bone marrow becomes less efficient at producing reticulocytes, despite persistent anaemia. This difference shows that we need more research to understand what affects bone marrow function in people with malaria over time. Is the bone marrow's ability to produce reticulocytes influenced by the duration of infection, or are there other underlying mechanisms that impair its function?

One of the central issues in the literature is the limited focus on comparing reticulocyte counts across varying levels of parasitemia. Most studies either focus on severe malaria or mild cases, leaving a gap in understanding the middle ground. Hence, the objective of this paper is to evaluate the haematological parameters and reticulocyte counts in children in fifty (50) children aged 5 to 12 years with various.

MATERIALS AND METHODS

Research Design/Study Area: This study adopts an observational research design to investigate the effect of malaria parasite infestation on reticulocyte values in children. The focus of the study is on children aged 5 to 12 years attending a tertiary teaching hospital (MUTH), in Elele, Rivers State, Nigeria.

Study Population: The study population comprised 50 children, both male and female, aged 5 to 12 years. This group included children diagnosed with malaria parasitemia and those without the parasite, forming two distinct comparison groups. The children were selected from those attending MUTH, providing a representative sample of the local paediatric population affected by malaria.

Inclusion and Exclusion Criteria: Inclusion in the study was limited to male and female children between the ages of 5 and 12 years. Eligible participants were those diagnosed with malaria infection but had not yet received any anti-malarial treatment. Children on any form of iron supplementation were excluded to avoid confounding effects on reticulocyte counts and haematological parameters. Additionally, children outside the specified age range were not included in the study.

Sample Collection Technique: A standard venipuncture technique was employed for blood sample collection. A 5ml sterile, dry plastic syringe, equipped with a 21-gauge needle, was used to collect blood samples from the participants. The collected blood sample was transferred into a container pre-prepared with Ethylene Diamine Tetraacetic Acid (EDTA) at a concentration of 1.2 mg/ml of blood. This anticoagulant was used to preserve the blood samples for further laboratory analyses, including haemoglobin estimation, packed cell volume (PCV), red blood cell count, malaria parasite identification, reticulocyte counting, and total white blood cell counting.

Procedures

Identification of Malaria Parasites: Thick blood films were allowed to air dry thoroughly. A 1:10 dilution of the stock Giemsa stain was prepared using buffered water. The prepared slide was flooded with the diluted Giemsa solution and left to stain for 10 minutes. Following this, the stain was washed off by immersing the slide in buffered water for 3 minutes. The slide was then allowed to air dry in a vertical position. Once dried, the stained film was examined under a microscope using an oil immersion objective. Parasite density was assessed and classified as mild, moderate, or severe based on the extent of parasitemia observed.

Hemoglobin Estimation: Two tubes were labelled "test" and "blank.". 4.0 ml of Drabkin's solution was mixed in the test tube with 0.02 ml of blood. The blank tube contained only 4.0 ml of Drabkin's solution. Both tubes were allowed to stand for five minutes. The spectrophotometer was calibrated using Drabkin's solution, and the absorbance of the test sample was read at 540 nm. The results were obtained using a haemoglobin calibration curve.

Packed Cell Volume (PCV) Determination: Anticoagulated blood was thoroughly mixed, and three-quarters of the capillary tube was filled with the sample. The open end of the tube was sealed with sealant material. The capillary tube was then centrifuged for five minutes at 12,000 rpm. After centrifugation, the PCV was read using a handheld microhematocrit reader. The red cell column was aligned with the zero mark, and the plasma column was aligned with the 100 mark. The PCV reading was taken from the scale, with the point of reference being the top of the red cell column, just beneath the buffy coat layer that contains white blood cells and platelets.

Total White Cell Count: First, 0.38 ml of diluting fluid was dispensed into a small tube. This was followed by the addition of 20 µl of well-mixed EDTA-anticoagulated venous blood, which was thoroughly mixed with the diluent. The counting chamber and hemocytometer cover glass were cleaned and dried before assembly. The cover glass was carefully placed over the grid areas and pressed down to create Newton's rings (rainbow colours), indicating proper positioning. The diluted blood sample was then re-mixed and, using a capillary tube held at an angle of approximately 45°, one of the grids in the chamber was filled, ensuring that the grid area was not overfilled. The chamber was left undisturbed for 2 minutes to allow the white cells to settle.Once settled, the underside of the chamber was dried, and the chamber was placed on the microscope stage. Using the $\times 10$ objective and closing the iris diaphragm for optimal contrast, the cells were focused until they appeared as small black dots. White cells in the four large corner squares (W1, W2, W3, and W4) were counted, including those along the lines of the two sides of each large square. The final result was expressed as the number of white cells counted per litre of blood, reported in units of $\times 10^9/L$. Upon completion of the count, the chamber was dismantled, washed, dried, and stored securely. Parasite density was calculated using Equation 1.

$$PD = \left(\frac{NPC}{WBC\ counted}\right) * WBC\ count\ per\ \mu L\ of\ blood \quad (1)$$

Where PD = parasite Density, NPC = number of parasite counted

Estimation of Reticulocyte Count: Two drops of an EDTA-anticoagulated blood sample were mixed with an equal volume of new methylene blue in a test tube. This mixture was incubated at 37°C for 15 minutes. After incubation, a thin blood film was prepared and allowed to air dry. The reticulocytes were then examined and counted using an $\times 100$ objective on a microscope.

Statistical Analysis: Data analysis was conducted using the Statistical Package for Social Sciences

(SPSS), version 20, compatible with Windows 7. The results were expressed as mean ± standard deviation (SD). Data obtained from the study were analysed using one-way analysis of variance (ANOVA) to compare means across groups. Statistical significance was established at $p < 0.05$, indicating that any differences were considered significant if the p-value was less than 0.05 and non-significant if $p < 0.05$.

RESULTS AND DISCUSSION

Presentation of Descriptive Data: The study involved participants classified into two groups: test subjects with malaria parasitemia and control subjects without parasitemia. The test subjects were further divided based on the severity of parasitemia into mild, moderate, and severe malaria categories. A total of 50 children were included, aged between 5 and 12 years, with an almost equal distribution of males and females. The control group had 15 participants, while the test group comprised 10 with mild malaria, 10 with moderate malaria, and 10 with severe malaria. Tables 1 and 2 provide the distribution and mean values of haematological parameters across the different categories.

Malaria Parasite Count Results: The parasite count was grouped based on the severity of parasitemia and the ANOVA results ($p < 0.05$) indicated that the parasite density increased with the severity of malaria. This statistical difference implies that parasite density likely increased as parasitemia severity progressed from mild to severe. The data (Table 2) on parasitemia severity (mild, moderate, severe) can be understood as a reflection of increasing parasite density. This trend reflects that severe malaria patients had the highest parasite load, while mild cases had lower counts.

Haematological Parameters: The results showed significant differences in haematological parameters between test and control groups, as well as among the varying levels of malaria severity, as shown in Tables 1 and 2.

Table 1: Mean values of the parameters in Malaria (test) subjects and non-malaria (control) subjects

Parameter	Test	Control	p-value
Reticulocyte (%)	3.1±1.12	2.0±0.82	P<0.05
PCV(L/L)	31.2±5.65	39.3±4.42	P<0.05
HB(g/dl)	10.2±1.9	12.9±0.83	P<0.05
TWBC(10^9/L)	8.3±2.38	6.9±1.84	P<0.05

Table 2: Mean values of the parameters in different groups

Parameter	Control	Mild	Moderate	Severe	p-value
Reticulocyte (%)	2.0±0.82	2.2±0.6	3.5±0.74	4.8±0.55	P<0.05
PCV(L/L)	39.3±4.4	34.8±3.85	28.5±5.6	26.1±2.99	P<0.05
HB(g/dl)	12.9±0.83	11.4±1.25	9.2±1.79	8.4±0.96	P<0.05
TWBC (10^9/L)	6.9±1.83	8.6±2.0	7.3±2.6	10.5±1.28	P<0.05

Packed Cell Volume (PCV): There was a significant decrease in the mean PCV of test subjects ($31.2 \pm 5.65\ L/L$) compared to the control group ($39.3 \pm 4.42\ L/L, (p < 0.05)$. Among the test subjects, PCV decreased progressively with the severity of malaria, with the lowest value recorded in the severe malaria group ($26.1 \pm 2.99\ L/L$).

Haemoglobin (Hb): A similar trend was observed for haemoglobin levels, with test subjects showing significantly lower Hb levels ($10.2 \pm 1.9\ g/dl$) compared to controls ($12.9 \pm 0.83\ g/dl, p < 0.05$). Severe malaria cases had the lowest Hb levels ($8.4 \pm 0.96\ g/dl$).

Reticulocyte Count: There was a significant increase in reticulocyte counts in the test group ($3.1 \pm 1.12\%$) compared to controls ($2.0 \pm 0.82\%, p < 0.05$). The count was highest in the severe malaria group ($4.8 \pm 0.55\%$) and lowest in the mild malaria group ($2.2 \pm 0.6\%$).

These findings suggest that malaria parasitemia significantly impacts haematological parameters, with more severe parasitemia correlating with greater reductions in PCV and Hb levels and an increase in the body's compensatory reticulocyte production.

Total White Blood Cell Count (WBC): The mean total white blood cell count (TWBC) was significantly different between the control and test groups ($p < 0.05$). Test subjects had a higher mean TWBC ($8.3 \pm 2.38 \times 10^9$/L) compared to controls ($6.9 \pm 1.84 \times 10^9$/L). Within the test group, subjects with severe malaria exhibited the highest WBC count ($10.5 \pm 1.28\ x10^9$/L), while moderate malaria subjects had lower values ($7.3 \pm 2.6 \times 10^9$/L).

The difference in WBC count between mild malaria and controls was also significant ($p < 0.05$), but there was no significant difference between controls and moderate malaria cases ($p < 0.05$).

Reticulocyte Count Results: The reticulocyte count exhibited a significant increase with the severity of malaria parasitemia. There was no significant difference between the control group and mild malaria cases ($p < 0.05$), but moderate and severe malaria cases showed significantly higher reticulocyte counts ($p < 0.05$). This suggests an adaptive bone marrow response to the anaemia induced by malaria infection.

The results of this study give important information about how children's blood reacts to different levels of malaria, especially how the bone marrow works and affects other blood measures. The main question of this research was whether knowing more about the bone marrow's response to malaria could help improve treatment for children. The results support the hypothesis that a significant relationship exists between malaria parasitemia and reticulocyte counts and that this relationship influences broader haematological parameters such as haemoglobin (Hb), packed cell volume (PCV), and total white blood cell count (TWBC).

As expected, it was observed a progressive increase in reticulocyte counts as the severity of parasitemia increased from mild to severe. This matches what other studies say, which is that malaria makes the bone marrow produce more reticulocytes because the parasite destroys red blood cells (Chang and Stevenson, 2004; Haldar and Mohandas, 2009b; Leowattana *et al.,* 2008; Paul and Brey, 2003; White, 2018). In this regard, reticulocyte production can be viewed as a compensatory mechanism aimed at maintaining erythrocyte homeostasis. However, this increased production does not necessarily translate into efficient recovery, as indicated by the concomitant decrease in haemoglobin levels and PCV across the different severity groups.

The results also provide evidence that malaria parasitemia is closely linked to changes in the TWBC, although the direction and magnitude of these changes vary across different levels of infection. The significant increase in TWBC in severe malaria cases suggests an inflammatory or immune response, which could be a reflection of the body's heightened attempt to fight the infection, showing that making reticulocytes isn't just the bone marrow's job. It's part of a bigger, more complex response where different parts of the body work together to fight malaria.

What remains thought-provoking is the obvious disconnect between the bone marrow's capacity to increase reticulocyte counts and the overall failure to prevent anaemia. This raises important questions: Is the reticulocyte response simply too slow to counter the rapid destruction of red blood cells? Or does severe malaria somehow impair the efficiency of the bone marrow's response, either through direct invasion or via inflammatory pathways? This could have profound implications for treatment strategies, particularly in paediatric populations where the balance between reticulocyte production and erythrocyte destruction is important for survival and recovery.

Effect of Malaria Parasitemia on Hematological Parameters: The haematological profile of children with malaria parasitemia shows a clear pattern of progressive anaemia as parasitemia severity increases, with significant reductions in haemoglobin (Hb) levels and packed cell volume (PCV) observed across the test groups. As detailed in Table 2, Hb and PCV levels decline steadily from the control group to those with mild, moderate, and severe malaria. The physiological basis for these reductions is in malaria's pathology, where *Plasmodium* parasites invade red blood cells (RBCs), leading to their destruction and subsequent hemolysis.

Correlation Between Parasitemia and Hemoglobin/PCV: The decrease in haemoglobin levels (from 12.9 g/dl in the control group to 8.4 g/dl in severe malaria) and PCV (from 39.3 L/L to 26.1 L/L) can be attributed to the parasite's direct destruction of RBCs. As Plasmodium species (Plasmodium falciparum) complete their life cycle inside RBCs, they cause the lysis of these cells upon maturation, leading to a marked reduction in erythrocyte count (Mohandas and An, 2012). The anaemia observed is not only a result of the parasite-induced destruction but also exacerbated by immune-mediated haemolysis, where the immune system targets infected and uninfected RBCs alike in an attempt to clear the parasite from circulation. The significant ($p < 0.05$). decline in PCV and Hb with increasing parasitemia is thus reflective of both mechanical destruction by parasites and immune-driven haemolysis.

Existing literature consistently supports the finding that malaria-induced anaemia results from these dual mechanisms of RBC destruction. Studies by Price *et al.* (2001) and other clinical trials conducted in sub-Saharan Africa have shown a strong correlation between parasitemia and decreased Hb levels in paediatric populations. This suggests that our findings align with the broader understanding of malaria pathology. However, the degree to which Hb and PCV decline in severe malaria cases within our

cohort may indicate regional or population-specific factors, such as genetic predispositions (e.g., G6PD deficiency or sickle cell trait), that further enhance haemolysis.

White Blood Cell Count and Immune Response: The results of this study reveal significant alterations in total white blood cell (WBC) count in response to varying degrees of malaria parasitemia. As shown in Table 2, there is a notable increase in WBC count as the severity of malaria infection progresses, with the control group exhibiting a mean count of $6.9 \times 10^9/\text{L}$ compared to $8.6 \times 10^9/\text{L}$, $7.3 \times 10^9/\text{L}$, and $10.5 \times 10^9/\text{L}$ for mild, moderate, and severe malaria cases, respectively. This rise in WBC count reflects the body's heightened immune response to the parasitic infection.

The immune system's primary role during malaria infection is to recognize and eliminate *Plasmodium* parasites. Leukocytes, including neutrophils, lymphocytes, and monocytes, play key roles in this defence (Dobbs *et al.*, 2020). In the early stages of malaria, a slight increase in WBCs is often seen as the immune system begins to respond to the infection (McKenzie *et al.*, 2005). This aligns with the modest rise in WBC count observed in mild malaria cases in this study ($8.6 \times 10^9/\text{L}$).

The immune response becomes more pronounced in severe malaria, which is marked by a significant increase in WBC count ($10.5 \times 10^9/\text{L}, (p < 0.05)$). This surge can be attributed to systemic inflammation and the activation of both innate and adaptive immune pathways to control the infection. In severe malaria, immune activation leads to increased production of cytokines, chemokines, and other signalling molecules that stimulate leukocyte production and mobilisation (Obeagu, 2024). Popa and Popa (2021) describe this inflammatory response as both protective and pathological, as it contributes to the clearance of the parasite but can also result in tissue damage and complications like cerebral malaria.

While our findings of increased WBC counts in severe malaria are consistent with the expected immune reaction, they contrast with reports of leukopenia commonly associated with mild malaria (Bartoloni and Zammarchi, 2012; Wynberg *et al.*, 2023). These differences could arise from regional or population differences, with factors such as the strain of *Plasmodium*, nutritional status, co-infections, and genetic predispositions influencing the immune response.

Significance of Reticulocyte Response: The increase in reticulocyte count observed in this study highlights the body's compensatory response to malaria-induced anaemia, as reflected by the significantly elevated reticulocyte percentages in malaria patients compared to controls ($3.1\% \pm 1.12$ vs $2.0\% \pm 0.82, (p < 0.05)$). As malaria parasites invade and destroy red blood cells (RBCs), the body initiates a compensatory mechanism by increasing erythropoiesis (the production of new red blood cells). This process is evident from the progressive rise in reticulocyte count across varying degrees of parasitemia, as shown in Table 4.2, where reticulocyte levels increase from 2.2% in mild malaria to 4.8% in severe cases.

Reticulocytes are immature RBCs released from the bone marrow into circulation in response to anaemia. The elevated reticulocyte counts seen in this study demonstrate that the bone marrow actively attempts to replace the RBCs destroyed by *Plasmodium* parasites. This compensatory mechanism is a natural response to hemolytic anaemia, which occurs due to the direct destruction of RBCs by the parasite and immune-mediated hemolysis, exacerbating the reduction in haemoglobin (HB) and packed cell volume (PCV). The reduction in HB and PCV, seen in both mild and severe malaria cases, indicates the severity of anaemia induced by malaria. For instance, severe malaria cases had a mean PCV of 26.1 L/L and HB of 8.4 g/dL, both significantly lower than the control group (39.3 L/L and 12.9 g/dL, respectively), as shown in Table 2.

Physiologically, this compensatory response is mediated by increased secretion of erythropoietin, a hormone produced by the kidneys in response to low oxygen levels in the blood, which stimulates the bone marrow to produce more RBCs. However, this compensatory response appears to be inadequate in children with high parasitemia levels, as the rise in reticulocyte count does not fully counteract the ongoing destruction of RBCs, as evidenced by the persistently low HB and PCV levels in these patients.

While the body's response is evident, it appears insufficient to keep up with the rapid destruction of RBCs in severe malaria. In children with high parasitemia, the reticulocyte count reached 4.8%, yet their HB and PCV levels remained critically low. This inadequate compensation can be attributed to several factors, including bone marrow suppression in severe malaria. (Ademola *et al.*, 2023; Awandare *et al.*, 2011) Argued in their studies that malaria-induced cytokine release, particularly elevated levels of tumour necrosis factor-alpha (TNF-α), interferes

with erythropoiesis. The inflammatory environment in severe malaria suppresses the production and maturation of new RBCs, rendering the bone marrow's response insufficient to meet the body's needs.

Reticulocyte Response to Malaria Treatment and Early Diagnosis: The reticulocyte response observed in this study underscores the critical importance of early malaria diagnosis and treatment to prevent severe anaemia. In the early stages of malaria, the body's compensatory mechanisms, including increased reticulocyte production, can help mitigate the effects of RBC destruction. However, as parasitemia levels rise, the bone marrow's capacity to produce reticulocytes becomes overwhelmed, and the anaemia worsens. This highlights the need for early intervention to reduce parasite load before severe anaemia develops. Effective malaria treatment aims to reduce the destruction of RBCs by rapidly clearing parasites from the bloodstream, allowing the bone marrow to catch up with the demand for new RBCs. Studies such as those by Ekvall (2003) have shown that prompt antimalarial treatment not only prevents severe anaemia but also improves the bone marrow's ability to restore normal RBC levels. Therefore, early diagnosis, particularly in vulnerable pediatric populations, is crucial to prevent the progression of parasitemia and subsequent anaemia.

Conclusion: Effective malaria treatment requires understanding the bone marrow response to parasitemia levels. This work helps explain the haematological effects of malaria in children and how reticulocyte synthesis reduces anaemia. The large rise in reticulocyte count shows the bone marrow's resilience to hemolytic stress, which may not entirely restore normal RBC levels in extreme cases. However, it shows the limits of this compensatory reaction, especially in severe parasitemia instances that require immediate medical treatment. Understanding the bone marrow's compensatory response to malaria-induced anaemia can help doctors intervene quickly, improving patient outcomes and decreasing severe anaemia morbidity.

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*Data Availability Statement:*Data are available upon request from the author

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