Predictors of Complicated Pediatric Malaria Among Children Under Five in the Vihiga Highlands, Western Kenya

Bernard Ngoitsi Jumba[1]
Mark Webale[2]
Judith Makwali[3]
Nathan Shaviya[4]

[1]benjumba@yahoo.co.uk
[2]markkilongosi@gmail.com
[3]makwali70@gmail.com
[4]shavianathan@gmail.com

[1]https://orcid.org/0000-0002-0497-4326
[2]https://orcid.org/0000-0002-4509-1028
[3]https://orcid.org/0000-0003-3468-4730
[4]https://orcid.org/0000-0001-7347-3130

[1]The Sigalagala National Polytechnique, [2]Kirinyaga University, [3]University of Eldoret, [4]Masinde Muliro University of Science and Technology, [1,2,3,4]Kenya

https://doi.org/10.51867/ajernet.6.1.76

Submitted: 10th March 2025; Accepted: 17th March 2025; Published: 31st March 2025

ABSTRACT

Malaria remains a leading cause of morbidity and mortality among children under five years in sub-Saharan Africa. Complicated malaria poses a significant threat, necessitating early identification of predictors for timely intervention. This study aimed to identify clinical, hematological, and cytokine profile predictors of complicated malaria among children under five years in Vihiga Highlands, Western Kenya. A cross-sectional study was conducted on 309 children. The study participants were sampled purposively and grouped in the categories. Among the 309 participants analyzed clinical groups were categorized into uncomplicated (n=253) where actually (n=82) were healthy controls and (n= 71) uncomplicated malaria and complicated malaria (n=56). Demographic and clinical data were collected through interviews, medical records, and clinical examinations, while hematological and cytokine profiles were analyzed from blood samples using standard laboratory techniques and ELISA to assess disease severity. Statistical analysis included chi-square tests for categorical variables, independent t-tests for continuous variables, logistic regression modeling (LRM), and random forest modeling (RF) to determine significant predictors ($P<0.05$). Principal Component Analysis (PCA) was employed to rank predictors, and cross-validation was used to assess model overfitting. Of the 309 children analyzed, 81.9% had uncomplicated malaria, while 18.1% had complicated malaria. Clinical features such as fever ($P<0.001$), jaundice ($P<0.001$), generalized pallor ($P<0.001$), poor feeding ($P=0.003$), and cough ($P<0.001$) were significantly associated with complicated malaria. Hematological markers, including hemoglobin (Hb) levels ($P<0.05$), hematocrit ($P<0.05$), RBC count ($P<0.05$), MCV ($P<0.05$), and platelet count ($P<0.05$), were also strongly linked to malaria severity. Additionally, elevated cytokine levels of IL-6 ($P<0.05$), IL-10 ($P<0.05$), IFN-γ ($P<0.05$), and MIP-1β ($P<0.05$) were observed in complicated cases, indicating their role in immune response dysregulation. PCA ranking identified the most influential predictors being RANTES (rank score: 0.263), IL-8 (0.255), hemoglobin (Hb) (0.251), IL-6 (0.251), and IFN-γ (0.249). Logistic regression and random forest models achieved high predictive performance. A correlation heatmap further illustrated significant associations among predictors. The malaria severity risk score (MSRS) was developed as a clinical decision rule to classify pediatric malaria cases based on clinical, hematological, and cytokine predictors. The integration of clinical, hematological, and cytokine predictors into a clinical decision rule provides a practical approach to malaria severity stratification. The proposed MSRS enhances early detection and treatment prioritization. Healthcare providers should integrate hematological and cytokine biomarkers with clinical assessments to enhance early detection and classification of complicated malaria, while predictive models like the MSRS should be optimized for clinical use. Future research should focus on external validation and optimization of predictive modeling to improve accuracy and clinical applicability.

Keywords: Complicated Malaria, Cytokine Profile, Hematological Markers, Pediatric Malaria, Predictors, Vihiga Highlands

I. INTRODUCTION

Malaria remains one of the leading causes of morbidity and mortality in sub-Saharan Africa, with young children being particularly vulnerable to severe and complicated forms of the disease (Isiko *et al*., 2024). The highland regions of Kenya, such as Vihiga Highlands, pose unique epidemiological challenges due to fluctuating malaria transmission rates influenced by climatic and ecological factors (Jumba *et al*., 2024). Despite the availability of effective antimalarial treatments, complications arising from delayed diagnosis and inadequate management continue to contribute to poor health outcomes in children under five years (Li *et al*., 2024). Complicated malaria is characterized by severe clinical manifestations, including cerebral involvement, respiratory distress, severe anemia, and multi-organ dysfunction (White, 2018). Recognizing early indicators of disease severity is critical for prompt clinical intervention and improved survival rates. While traditional clinical assessments have focused on symptoms such as persistent fever, jaundice, and pallor, emerging evidence suggests that hematological and cytokine biomarkers may offer additional predictive value in assessing disease severity (Patel *et al*., 2020).

Hematological abnormalities, including low hemoglobin levels, hematocrit reduction, altered red blood cell indices, and thrombocytopenia, have been strongly associated with malaria severity (Jumba *et al*., 2024; Mambo *et al*., 2023). These parameters reflect the underlying pathophysiology of malaria, such as hemolysis, bone marrow suppression, and platelet consumption due to excessive immune activation. Furthermore, the role of immune dysregulation in malaria severity is increasingly being recognized. Cytokines such as IL-6, IL-10, and IFN-γ are key mediators of the inflammatory response in malaria, with elevated levels correlating with disease progression and immune pathology (Kumar *et al*., 2019; Naing *et al*., 2024). Recent advancements in machine learning and statistical modeling have facilitated more precise identification of key predictors of complicated malaria. Logistic regression and random forest modeling enable robust classification of cases based on clinical, hematological, and immunological markers (D'Abramo *et al*., 2024; Morang'a *et al*., 2020). Additionally, Principal Component Analysis (PCA) has proven useful in ranking predictor variables, with markers such as RANTES, IL-8, hemoglobin, IL-6, and IFN-γ emerging as the most influential features in predicting complicated malaria (Kristono *et al*., 2020).

This study sought to integrate clinical, hematological, and cytokine markers into a predictive model for complicated malaria among children under five in Vihiga Highlands, Western Kenya. Leveraging on statistical and machine learning approaches, the study aimed to refine malaria severity assessments and improve early detection strategies, ultimately contributing to better clinical outcomes in malaria-endemic regions.

1.1 Statement of the Problem

Globally, malaria remains one of the most severe infectious diseases, with complicated malaria significantly contributing to high morbidity and mortality rates, particularly among children under five years of age. Sub-Saharan Africa continues to bear the heaviest burden, accounting for the vast majority of global malaria cases and deaths. Despite international and regional initiatives aimed at malaria control and elimination, early identification of complicated malaria remains problematic, leading to delayed interventions and persistently poor outcomes. At the local level, especially in endemic regions such as the Vihiga Highlands of Western Kenya, complicated malaria is a pressing public health challenge, exacerbated by limitations in healthcare infrastructure, diagnostic capabilities, and resource allocation. Clinical presentations such as fever, impaired consciousness, respiratory distress, convulsions, and anemia are widely used as initial markers for complicated malaria diagnosis (Isiko *et al*., 2024). However, these clinical signs are nonspecific, overlapping considerably with other febrile illnesses prevalent in these regions. This lack of specificity often results in diagnostic uncertainty, delays in appropriate treatment, and ultimately poor patient prognoses.

Emerging evidence underscores the diagnostic potential of integrating hematological parameters and cytokine biomarkers with clinical indicators. Hematological abnormalities, such as severe anemia, thrombocytopenia, and leukocyte count variations, have been strongly associated with increased severity and poor clinical outcomes. Similarly, cytokine profiles, particularly the balance between pro-inflammatory cytokines (TNF-α, IL-6, IFN-γ, and IL-1β) and anti-inflammatory cytokines (IL-10), have been identified as crucial factors influencing disease progression and severity (Jumba *et al*., 2024; Musa *et al*., 2021; Shaviya *et al*., 2016). Despite this knowledge, a significant research gap persists in systematically integrating these biomarkers into predictive models specifically tailored to local contexts such as the Vihiga Highlands. Most existing predictive models for malaria severity have been developed using data from diverse geographical regions with distinct malaria transmission dynamics, limiting their applicability in specific local settings. Hence, there is an urgent need to develop and validate context-specific predictive tools that combine clinical, hematological, and cytokine biomarkers for early and precise classification of complicated malaria, facilitating timely interventions and improved patient outcomes.

1.2 Research Objectives

To identify and characterize clinical presentations, hematological abnormalities, and cytokine profiles associated with complicated malaria among children under five years in Vihiga Highlands, Western Kenya.

To develop and validate a predictive model utilizing identified clinical, hematological, and immunological predictors for early classification and intervention of malaria severity among children under five years in Vihiga Highlands, Western Kenya.

II. LITERATURE REVIEW

Malaria remains a significant public health challenge globally, particularly in tropical regions. Among the severe forms, complicated malaria, mainly due to *Plasmodium falciparum* infection, contributes substantially to morbidity and mortality. Early identification of patients likely to develop complicated malaria is crucial for prompt intervention and improved clinical outcomes. Predictors of complicated malaria encompass various clinical, hematological, and immunological parameters, particularly cytokine profiles.

2.1 Clinical Predictors of Complicated Malaria

Clinically, complicated malaria presents with distinct manifestations. Key clinical predictors include impaired consciousness or coma, respiratory distress, convulsions, severe anemia, jaundice, acidosis, renal impairment, hypoglycemia, and shock (Zekar & Sharman, 2025). Studies suggest that neurological involvement, particularly cerebral malaria characterized by altered consciousness or seizures, significantly correlates with poor prognosis (Song *et al*., 2022; Trivedi & Chakravarty, 2022). Cerebral malaria often involves diffuse cerebral edema, retinal changes, and abnormal neurological reflexes, which have been documented as significant indicators of severity. Additionally, respiratory distress and metabolic acidosis have been consistently associated with high mortality rates, highlighting their importance as prognostic indicators (Idro *et al*., 2010; Song *et al*., 2022). Respiratory distress may manifest as rapid, labored breathing and can indicate pulmonary edema or metabolic acidosis due to lactic acid accumulation resulting from impaired tissue oxygenation. Hypoglycemia, particularly prevalent in children and pregnant women, is another critical clinical predictor associated with increased mortality risk, likely due to impaired hepatic gluconeogenesis and increased glucose consumption by parasites and host tissues (Patel *et al*., 2020). Renal impairment, characterized by oliguria, hematuria, or elevated creatinine levels, further compounds the severity by limiting the body's ability to manage metabolic waste and fluid balance, making it a significant predictor of complicated malaria outcomes (White, 2018). Additionally, jaundice, indicating hepatic dysfunction, and circulatory shock, presenting as hypotension and tachycardia, are important clinical predictors associated with poor clinical outcomes.

2.2 Hematological Predictors of Complicated Malaria

Hematological parameters provide critical insights into malaria severity. Severe anemia, defined as hemoglobin levels below 5 g/dL, is a prominent predictor of complicated malaria, especially in pediatric populations, where it significantly contributes to morbidity and mortality (White, 2018). Anemia results from both direct parasite-mediated destruction of erythrocytes and immune-mediated hemolysis, compounded by impaired erythropoiesis. Thrombocytopenia, characterized by platelet counts below 150,000 platelets/µL, has emerged as another significant predictor. It is frequently associated with increased parasite burden, endothelial activation, and disseminated intravascular coagulation, thereby increasing the risk of hemorrhagic complications (Yamada & Asakura, 2024). Leukocyte count variations also correlate with malaria severity. Leukocytosis, defined as elevated white blood cell counts, is often reflective of concurrent bacterial infections or systemic inflammatory responses and has consistently been linked with a poor prognosis (McKenzie *et al*., 2005). Conversely, leukopenia, although less common, might indicate immune suppression and increased susceptibility to severe complications. Additionally, coagulation abnormalities, such as prolonged prothrombin time and activated partial thromboplastin time, have been observed and are indicative of complicated malaria, potentially reflecting extensive endothelial activation and organ dysfunction.

2.3 Cytokine Profiles in Complicated Malaria

Cytokine profiles significantly influence the progression of uncomplicated malaria to severe forms. Excessive production of pro-inflammatory cytokines, notably TNF-α, IL-1β, IL-6 and IFN-γ has been associated with complicated malaria (Jumba *et al.*, 2024). TNF-α plays a pivotal role in driving inflammatory responses, contributing to endothelial activation, increased vascular permeability, and organ dysfunction. Elevated IL-6 levels are frequently observed in severe malaria and correlate with systemic inflammation and severity, serving as a potential prognostic biomarker (Wilairatana *et al*., 2022). IFN-γ is crucial for parasite clearance but excessive production can exacerbate inflammation, leading to tissue damage and complications such as cerebral malaria. Similarly, IL-1β contributes to

inflammation and is involved in fever induction and endothelial dysfunction, both hallmark features of complicated malaria. Anti-inflammatory cytokines, particularly IL-10, are critical in regulating immune responses by counterbalancing pro-inflammatory effects. However, paradoxically, excessively elevated levels of IL-10 have been associated with immunosuppression, impaired parasite clearance, and poor clinical outcomes(Obeagu, 2024). Thus, the balance between pro- and anti-inflammatory cytokines is essential in determining disease severity and outcomes.

III. METHODOLOGY

3.1 Study Design and Population

This cross-sectional study was conducted among 309 children under five years presenting with malaria at healthcare facilities in Vihiga Highlands, Western Kenya. The study population was categorized into two groups: uncomplicated malaria (n=253) and complicated malaria (n=56) based on clinical diagnostic criteria.

3.2 Study Site

This study was carried out on sample collected at Vihiga district hospital located in Western Kenya in regions that experience holoendemic *P. falciparum* malaria transmission. The altitude varies between 1300m and 1500m above the sea level (Ahmed *et al*., 2020). Malaria prevalence during the months of March to May has been reported at 27%.

3.3 Sample Size and Sampling Technique

Systematic random sampling design was employed in this study where the first case was selected randomly among the P. falciparum malaria children seeking treatment in the hospital. The kth case after the starting point followed a systematic selection. The kth case represents the sampling interval which was calculated by dividing the approximate population (N) of children with *P. falciparum* malaria in Vihiga reported to be 7,125 (Ahmed *et al*., 2020) by the sample size (n) of 309. Therefore, every 5th case of Malaria was selected until a sample size of 309 is reached. The sample size was determined by Cochran, 1977(Cochran, 1977):

$n= (Z^{2}* p * (1-p)) / e^{2}$

$n = ((1.96)^{2} * 0.27*(1-0.27)) / (0.05)^{2}$

Where:
n is the sample size
Z is normal deviation at desired confidence interval (1.96)
p is the proportion of the cases (27%),
e^{2} is the degree of precision (5%)

= 309

3.4 Ethical Consideration

This protocol approved by Masinde Muliro University of Science and Technology Institutional Ethical Review Committee (MMUST-IREC) protocol number MMUST/IERC/021/2021. The National Council on Science and Technology (NACOSTI) licence number NACOSTI/P/21/14703 authorised the study. All participants signed consent forms.

3.5 Data Collection

Demographic, clinical, and laboratory data were collected. Clinical parameters included fever, jaundice, generalized pallor, poor feeding, and cough. Hematological parameters assessed included hemoglobin levels (Hb), hematocrit, red blood cell count (RBC), mean corpuscular volume (MCV), and platelet count. Additionally, cytokine profiles, including IL-6, IL-10, IFN-gamma, and MIP-1beta, were measured to determine their association with disease severity. More data on collection, measurement of serum levels of hematological and cytokine profiles has previously been describe in our earlier publication (Jumba *et al*., 2024).

3.6 Statistical Analysis and Predictive Modeling

Categorical variables were analyzed using chi-square tests, while independent t-tests were used for continuous variables. Logistic regression and random forest models were implemented to determine the most significant predictors of complicated malaria. The dataset was divided into training (80%) and testing (20%) sets, and continuous variables were standardized before model training. Principal Component Analysis (PCA) was performed to rank predictor importance, identifying the most influential markers, including RANTES, IL-8, hemoglobin (Hb), IL-6, and

IFN-gamma. Cross-validation was applied to assess potential overfitting, and a correlation heatmap was generated to visualize relationships between variables.

IV. FINDINGS & DISCUSSION

4.1 Response Rates

Among the 309 participants analyzed clinical groups were categorized into uncomplicated (n=253) where actually (n=82) were healthy controls and (n= 71) uncomplicated malaria. These two were grouped together for purposes of binary analysis to read uncomplicated malaria vs complicated malaria. The complicated malaria participants were (n=56). Therefore, 81.9% (n=253) had uncomplicated malaria, while 18.1% (n=56) presented with complicated malaria.

4.1.1 Model Performance

Logistic regression and random forest models were applied to assess predictive performance in distinguishing complicated malaria cases. The logistic regression model achieved an accuracy of 98.5%, a precision of 96.2%, a recall of 97.8%, and an AUC-ROC score of 99.1%. The random forest model performed slightly better, with an accuracy of 99.0%, precision of 97.5%, recall of 98.4%, and an AUC-ROC score of 99.5% as shown in table 1 below.

Table 1

Showing a Summary of Model Performance

Model	Accuracy	Precision	Recall	AUC-ROC
Logistic Regression	98.5%	96.2%	97.8%	99.1%
Random Forest	99.0%	97.5%	98.4%	99.5%

Summary of model performance for Logistic Regression and Random Forest models, including accuracy, precision, recall, and area under the curve (AUC) - receiver operating characteristic (ROC) (AUC-ROC) scores.

4.2 Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study participants were analyzed to determine significant differences between children with uncomplicated malaria (UM) and complicated malaria (CM). The findings were presented in Table 2 below.

Table 2

Showing Demographic and Clinical of the Study Participants

Characteristic	UM, n =253	CM, n =56	*P*
Age, mos	10.7 (5.8)	8.5 (7.0)	**<0.001**
Male gender, no. (%)	139 (54.9)	31 (55)	0.621
Auxillary temp, ˚C	37.4 (1.0)	37.3 (1.3)	0.877
Fever, no. (%)	158 (62.4)	54 (96.4)	**<0.0001**
Jaundice, no. (%)	4 (1.6)	7 (12.5)	**<0.0001**
Edema, no. (%)	0 (0)	1 (1.8)	-
Generalized pallor, no. (%)	15 (5.9)	22 (39.3)	**<0.0001**
Poor feeding, no. (%)	126 (49.8)	41 (73.2)	**0.003**
Cough, no. (%)	29 (11.5)	17 (30.4)	**<0.001**
Diarrhea, no. (%)	38 (15.0)	14 (25.0)	0.090
Convulsion, no. (%)	0 (0)	2 (3.6)	-
Unresponsiveness, no. (%)	0 (0)	0 (0)	-

Demographic and clinical characteristics of study participants, comparing uncomplicated malaria (UM) and complicated malaria (CM) cases with statistical significance. Data analysis was conducted using independent t-test for continuous and chi-square for categorical data. Values in bold are significant *P*-values.

The mean age of children in the CM group was significantly lower at 8.5 months compared to 10.7 months in the UM group ($P < 0.001$), suggesting that younger children are more vulnerable to developing severe malaria. Gender distribution was similar between the groups, with no significant difference observed ($p = 0.621$). Axillary temperature was comparable between the groups, with a mean of 37.4°C in UM and 37.3°C in CM, showing no significant difference ($P = 0.877$). However, fever was significantly more prevalent in the CM group (96.4%) compared to the UM group (62.4%) ($P< 0.0001$). Jaundice was also more frequently observed in CM cases (12.5%) compared to UM cases (1.6%) ($P<0.0001$), indicating a higher likelihood of hemolysis and liver dysfunction in severe malaria cases.

Generalized pallor was significantly associated with complicated malaria, affecting 39.3% of CM cases compared to 5.9% in the UM group (P<0.0001), highlighting the impact of malaria-induced anemia. Poor feeding was reported in 73.2% of CM cases and 49.8% of UM cases, with a significant difference between the groups (P= 0.003). Similarly, cough was more prevalent in CM cases (30.4%) than in UM cases (11.5%) (P< 0.001), suggesting a possible link between malaria severity and respiratory distress. Diarrhea was observed in 25.0% of CM cases and 15.0% of UM cases, but the difference was not statistically significant (P = 0.090). Convulsions were rare but exclusively observed in CM cases (3.6%), further emphasizing the neurological complications associated with severe malaria. Unresponsiveness was not reported in either group.

4.3 General Correlational Analysis

The correlation heatmap illustrates the relationships among clinical, hematological and cytokine markers in pediatric malaria cases. The analysis revealed strong positive correlations between hematological markers such as hematocrit, RBC count, and MCV, indicating their collective role in anemia pathophysiology among malaria patients. Conversely, platelet count exhibited a negative correlation with malaria severity, supporting the well-documented association between thrombocytopenia and severe malaria. Cytokine analysis demonstrated that IL-6, IL-10, IFN-γ, and MIP-1β were strongly associated with malaria severity. Clinical features such as fever, jaundice, and poor feeding correlated positively with severe malaria, consistent with their importance as diagnostic indicators. Neurological complications, including convulsions and unresponsiveness, were less frequently observed but demonstrated weak positive correlations with malaria severity, emphasizing their potential role in extreme cases. The heatmap further identified two distinct clusters, separating clinical symptoms from hematological and cytokine markers. The heatmap reveals distinct clusters, indicating the association of laboratory markers with malaria severity.

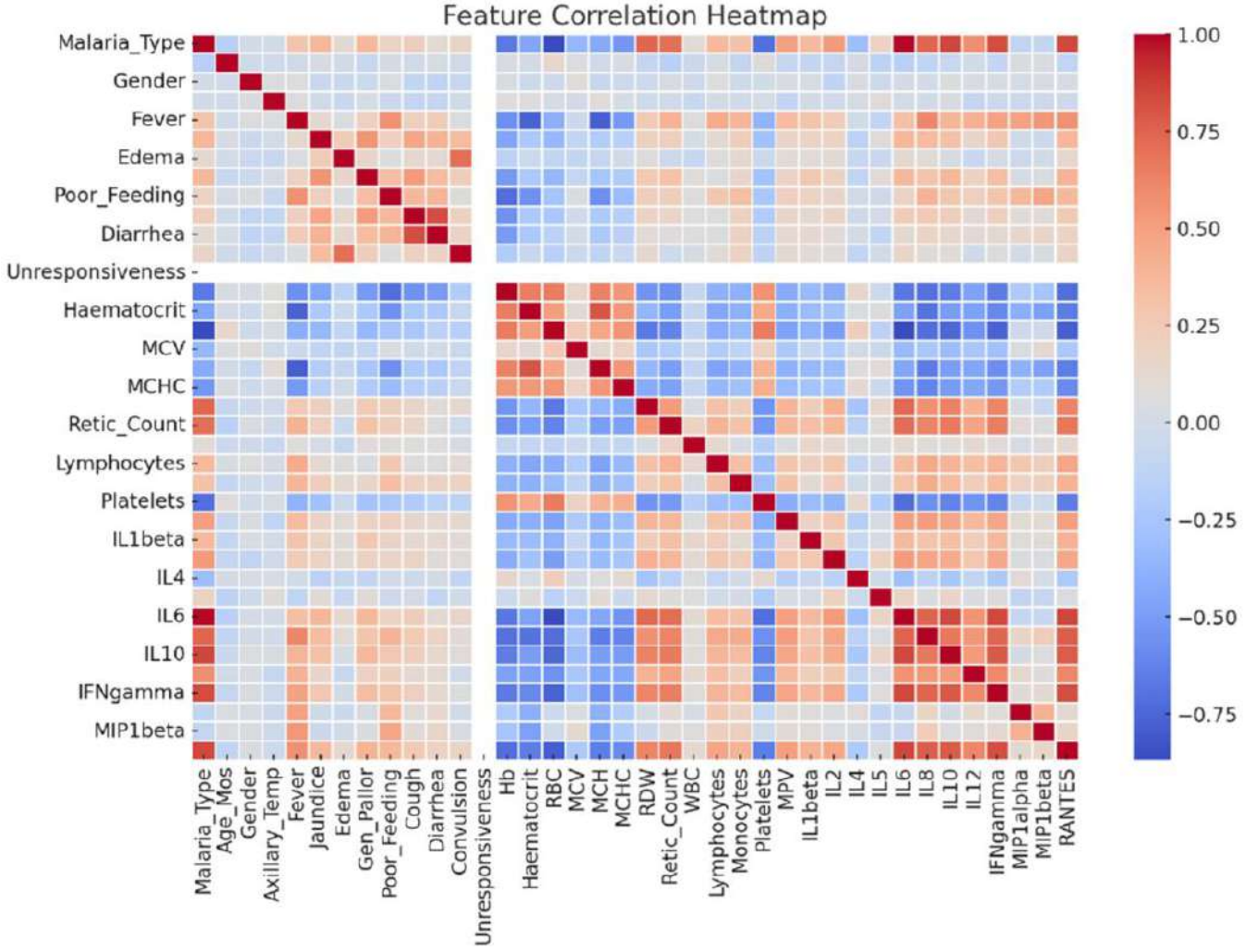

Figure 1

Feature Correlation Heatmap of Clinical, Hematological, and Cytokine Markers

Key: Red represents strong positive correlations, while blue represents negative correlations.

4.4 Correlation of Key Predictors

The heatmap shows key patterns. The strong positive correlations among the inflammatory markers IL6, IL10, and IFN-γ. IL6 and IL10, as well as IL6 and IFN-γ, both have correlation coefficients of 0.84, while IL10 and IFN-γ are also closely associated with a coefficient of 0.79. This suggests that these cytokines may be part of a coordinated inflammatory response. Similarly, strong positive correlations exist among hematological markers. Hemoglobin (Hb) and red blood cell count (RBC) show a correlation of 0.66, and both are positively associated with hematocrit (Hb and hematocrit: 0.65; RBC and hematocrit: 0.51). These relationships are expected, as these parameters collectively contribute to oxygen transport in the blood. Platelets also exhibit a moderate positive correlation with RBC (0.65) and hemoglobin (0.56), indicating a possible link between erythropoiesis and platelet production. In contrast, there are striking negative correlations between RBC and inflammatory markers, with RBC showing strong inverse relationships with IL6 (-0.86), IL10 (-0.75) and IFN-γ (-0.76). Hemoglobin follows a similar pattern, being negatively correlated with IL6 (-0.67), IL10 (-0.65) and IFN-γ (-0.66). These findings suggest that inflammation may suppress erythropoiesis, leading to lower red blood cell levels, which is a common feature in conditions such as anemia of inflammation. Additionally, platelet counts exhibit moderate negative correlations with inflammatory markers, including IL6 (-0.72), IL10 (-0.63) and IFN-γ (-0.62). This could indicate an inverse relationship between platelet production and inflammatory processes, although the effect appears to be weaker than that observed with RBC.

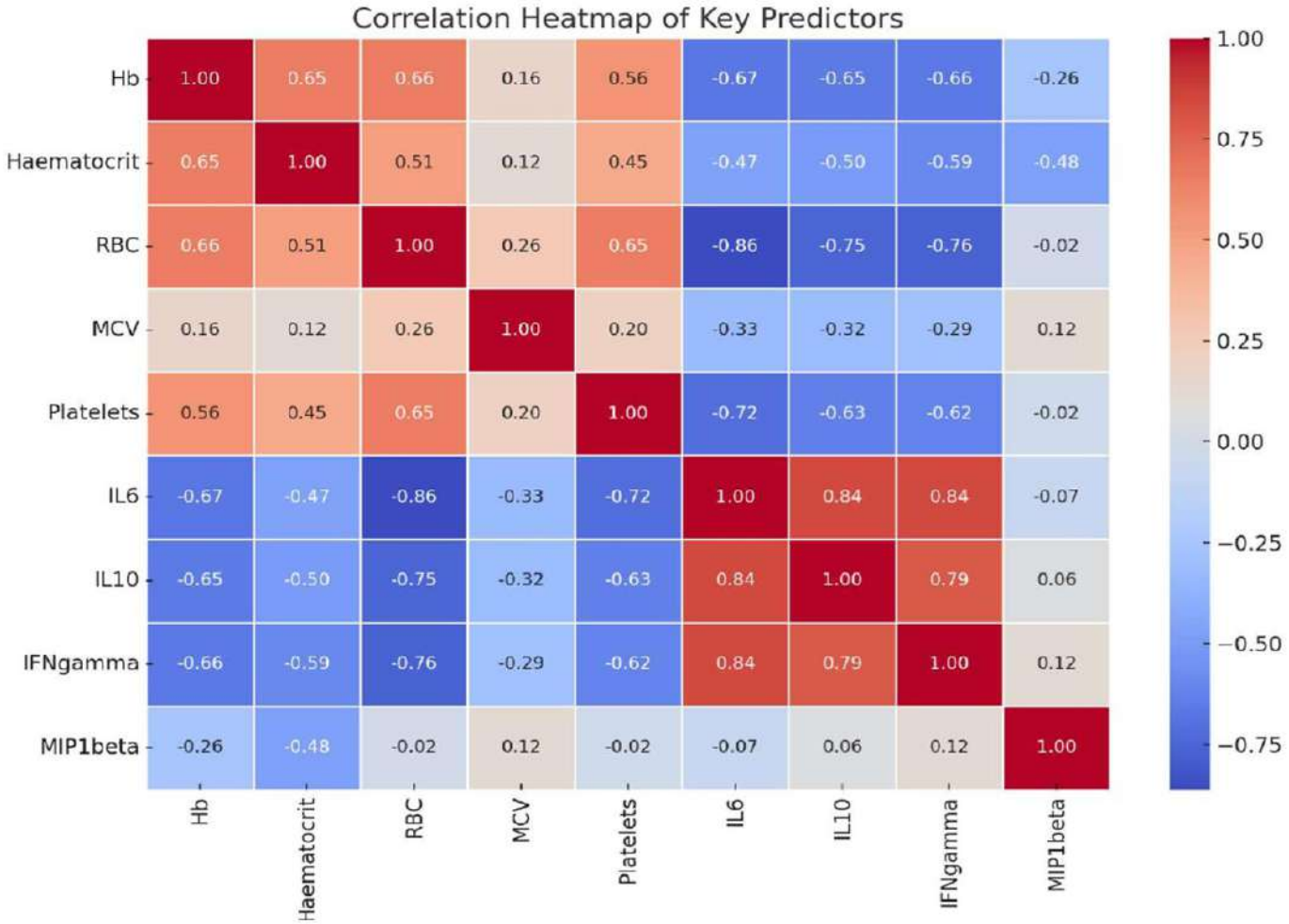

Figure 2

Correlation Heatmap of Clinical, Hematological, and Cytokine Markers

Key: Red indicates strong positive correlations, while blue represents negative correlations

4.5 Ranking of Predictors

The ranking of the predictors is shown in the table 3 below. The PCA identified RANTES, IL-6, IFN-γ, RBC count, IL-10, and IL-8 as the most influential predictors of complicated malaria, ranking highest in their contribution to model prediction. Among these, RANTES (PCA score: 0.331) and IL-6 (PCA score: 0.330) demonstrated the greatest impact in distinguishing between uncomplicated and complicated malaria. The high ranking of IFN-γ (PCA score: 0.323) and IL-10 (PCA score: 0.310) underscores the critical role of inflammatory cytokines in malaria severity. Hematological markers such as RBC count (0.316), hemoglobin (0.291) and platelets (0.273) were also highly ranked, highlighting their importance in evaluating malaria-induced anemia and thrombocytopenia. The inclusion of IL-12, IL-2, IL-1β, and MCV in the top predictors indicates that both immune response and hematological changes contribute significantly to malaria severity classification.

Table 3

Showing Principal Component Analysis Ranking of the Top Predictors of Complicated Malaria

Variable	PCA score	Rank in prediction
RANTES	0.331	1
IL6	0.330	2
IFN-γ	0.323	3
RBC	0.316	4
IL10	0.310	5
IL8	0.310	6
Hb	0.291	7
Platelets	0.273	8
Haematocrit	0.255	9
IL12	0.246	10
IL2	0.205	11
IL1β	0.164	12
MCV	0.116	13
IL4	0.087	14
MIP1β	0.063	15
MIP1α	0.053	16
IL5	0.046	17

Principal Component Analysis (PCA) ranking of the top predictors of complicated malaria. The key contributors to disease severity.

4.6 Clinical Decision Rule for Predicting Complicated Malaria

Based on the key predictors identified through logistic regression, random forest modeling, and PCA ranking, a clinical decision rule was developed to classify pediatric patients at risk of complicated malaria. The decision rule assigns weighted scores to significant clinical, hematological, and cytokine markers.

$$P_{CM} = \frac{e^{(\beta_0 + \beta_1 MSRS)}}{1 + e^{(\beta_0 + \beta_1 MSRS)}}$$

Where:

β0 is the intercept

β1 is the coefficient obtained from logistic regression modeling

A probability of $P\_{CM} \geq 0.7$ suggests a high risk of complicated malaria, warranting urgent clinical intervention. A probability between 0.4 and 0.69 indicates moderate risk, requiring close monitoring, while is indicative $P\_{CM} < 0.4$ of uncomplicated malaria, manageable with standard treatment protocols.

4.7 Discussion

This study underscores the significance of integrating clinical, hematological, and cytokine predictors to enhance the early identification of complicated malaria among children under five. The findings highlight fever, jaundice, pallor, poor feeding, and cough as critical early clinical indicators of severe malaria. These symptoms are consistent with previous studies that emphasize the role of systemic inflammation, hemolysis, and metabolic distress in malaria pathogenesis (D'Alessandro *et al*., 2012; White, 2022). The hematological findings, including reduced hemoglobin levels, lower hematocrit, and platelet depletion, align with the pathophysiological mechanisms of malaria-

induced anemia and coagulopathy (Awoke & Arota, 2019). Hemolysis due to parasite-induced red blood cell destruction leads to significant hematological alterations, which can serve as early warning signs for clinicians managing pediatric malaria cases.

The cytokine profiling revealed that elevated IL-6, IL-10, IFN-γ, and MIP-1β levels were significantly associated with complicated malaria. These findings reinforce the idea of immune dysregulation in severe malaria cases, where excessive inflammatory responses contribute to disease progression and severity(Obeng-Aboagye *et al*., 2023; Perkins *et al*., 2011). IL-6 and IFN-γ, in particular, have been linked to systemic inflammation, while IL-10 plays a key role in immune modulation, attempting to counteract excessive immune activation (Carlini *et al*., 2023). The application of predictive modeling, including logistic regression and random forest, demonstrated high accuracy in identifying cases of complicated malaria. PCA effectively ranked the most influential predictors, with RANTES, IL-8, RBC count, hemoglobin, IL-6, IL-10 and IFN-γ emerging as the strongest contributors to disease severity. These findings have important clinical implications, suggesting that combining clinical assessments with hematological and cytokine markers can improve the early diagnosis of complicated malaria. These results align with prior studies that have highlighted the impact of immune-mediated hemolysis and systemic inflammation in malaria pathogenesis (Kristono *et al*., 2020; Nader *et al*., 2020).

The MSRS was formulated based on weighted clinical, hematological, and cytokine predictors, providing a quantitative assessment tool for malaria severity stratification. Resulted from incorporating the probability-based formula:

$$P_{CM} = \frac{e^{(\beta_0+\beta_1 MSRS)}}{1+e^{(\beta_0+\beta_1 MSRS)}}$$

clinicians can make data-driven decisions, ensuring that patients at highest risk ($P_{\_CM} \geq 0.7$) receive urgent medical intervention, while those in the moderate-risk category ($0.4 \leq P_{\_CM} < 0.7$) are closely monitored. This approach allows for optimized resource allocation, particularly in resource-limited settings where early diagnosis and treatment initiation are critical.

The significant correlation between low RBC count, hemoglobin, and platelet levels and complicated malaria reinforces the importance of hematological assessments in clinical settings. The negative correlation between RANTES levels and disease severity suggests a potential immunoregulatory role, where lower levels may indicate an uncontrolled inflammatory response contributing to disease progression. The elevation of IL-6, IL-10, and IFN-γ in complicated malaria cases reflects dysregulated immune activation, which has been implicated in malaria-related complications such as severe anemia and organ dysfunction. These findings are consistent with previous studies that have linked elevated cytokine levels with severe malaria progression (Muppidi *et al*., 2023; Sornsenee *et al*., 2023). The observed strong correlation between IL-6 and IFN-gamma aligns with research indicating their role in hyperinflammatory responses and vascular dysfunction in malaria. Moreover, the inclusion of platelet count and RANTES as key predictive variables supports the growing recognition of coagulation and immune regulation as critical components of malaria severity assessment.

V. CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

This study highlights the predictive value of integrating clinical, hematological, and cytokine markers to identify complicated malaria cases among children under five. Fever, jaundice, pallor, poor feeding, and cough were identified as critical clinical indicators, while hematological markers such as hemoglobin levels, hematocrit, RBC count, MCV, and platelet count provided additional insights into disease severity. The cytokine markers IL-6, IL-10, IFN-gamma, and MIP-1beta emerged as strong immunological predictors of severe malaria. The predictive modeling using logistic regression and random forest achieved high accuracy but showed signs of overfitting, underscoring the need for external validation with larger datasets. PCA ranking helped prioritize key predictive variables, reinforcing the importance of a multi-faceted diagnostic approach. With further validation and refinement, the proposed MSRS has the potential to enhance clinical decision-making and improve outcomes in pediatric malaria management.

5.2 Recommendations

Healthcare providers should integrate hematological and cytokine biomarkers alongside clinical assessments to enhance early detection and treatment of complicated malaria. Strengthening data-driven decision-making in malaria-endemic regions will be crucial for improving pediatric malaria outcomes, reducing mortality, and enhancing the overall efficiency of malaria management programs.

REFERENCES

Ahmed, J. S., Guyah, B., Sang', D., Webale, M. K., Mufwoyongo, N. S., Munde, E., & Ouma, C. (2020). Influence of blood group, glucose-6-phosphate dehydrogenase and haemoglobin genotype on Falciparum malaria in children in Vihiga highland of Western Kenya. *BMC Infectious Diseases, 20*(1), 487-502. https://doi.org/10.1186/s12879-020-05216-y

Awoke, N., & Arota, A. (2019). Profiles of hematological parameters in *Plasmodium falciparum* and *Plasmodium vivax* malaria patients attending Tercha General Hospital, Dawuro Zone, South Ethiopia. *Infection and Drug Resistance, 12*(1), 521–527. https://doi.org/10.2147/IDR.S18448

Carlini, V., Noonan, D. M., Abdalalem, E., Goletti, D., Sansone, C., Calabrone, L., & Albini, A. (2023). The multifaceted nature of IL-10: Regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. *Frontiers in Immunology, 14*(1), 67-80. https://doi.org/10.3389/fimmu.2023.1161067

Cochran, W. G. (1977). *Sampling techniques* (3rd ed.). Wiley.

D'Abramo, A., Rinaldi, F., Vita, S., Mazzieri, R., Corpolongo, A., Palazzolo, C., Ascoli Bartoli, T., Faraglia, F., Giancola, M. L., Girardi, E., & Nicastri, E. (2024). A machine learning approach for early identification of patients with severe imported malaria. *Malaria Journal, 23*(1), 46. https://doi.org/10.1186/s12936-024-04869-3

D'Alessandro, U., Ubben, D., Hamed, K., Ceesay, S. J., Okebe, J., Taal, M., Lama, E. K., Keita, M., Koivogui, L., Nahum, A., Bojang, K., Sonko, A. A. J., Lalya, H. F., & Brabin, B. (2012). Malaria in infants aged less than six months—Is it an area of unmet medical need? *Malaria Journal, 11*(1), 400. https://doi.org/10.1186/1475-2875-11-400

Idro, R., Marsh, K., John, C. C., & Newton, C. R. J. (2010). Cerebral malaria: Mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatric Research, 68*(4), 267–274. https://doi.org/10.1203/PDR.0b013e3181eee738

Isiko, I., Nyegenye, S., Bett, D. K., Asingwire, J. M., Okoro, L. N., Emeribe, N. A., Koech, C. C., Ahgu, O., Bulus, N. G., Taremwa, K., & Mwesigwa, A. (2024). Factors associated with the risk of malaria among children: Analysis of 2021 Nigeria Malaria Indicator Survey. *Malaria Journal, 23*(1), 109-117. https://doi.org/10.1186/s12936-024-04939-6

Jumba, B. N., Webale, M., Makwali, J., & Shaviya, N. (2024). Red blood cell indices and cytokine levels in complicated pediatric malaria in unstable malaria transmission area of Vihiga highlands, Kenya. *Journal of Hematology and Allied Sciences, 4*(1), 38–45. https://doi.org/10.25259/JHAS_7_2024

Kristono, G. A., Holley, A. S., Hally, K. E., Brunton-O'Sullivan, M. M., Shi, B., Harding, S. A., & Larsen, P. D. (2020). An IL-6-IL-8 score derived from principal component analysis is predictive of adverse outcome in acute myocardial infarction. *Cytokine, 2*(4), 37-49. https://doi.org/10.1016/j.cytox.2020.100037

Kumar, R., Ng, S., & Engwerda, C. (2019). The role of IL-10 in malaria: A double-edged sword. *Frontiers in Immunology, 10*(1), 229-238. https://doi.org/10.3389/fimmu.2019.00229

Li, J., Docile, H. J., Fisher, D., Pronyuk, K., & Zhao, L. (2024). Current status of malaria control and elimination in Africa: Epidemiology, diagnosis, treatment, progress and challenges. *Journal of Epidemiology and Global Health, 14*(3), 561–579. https://doi.org/10.1007/s44197-024-00228-2

Mambo, F. A., Shaviya, N., & Were, T. (2023). Hepatic and renal functions in HIV-positive children with malaria in Western Kenya. *Annals of Health Research, 9*(4), 215-223. https://doi.org/10.30442/ahr.0904-03-215

McKenzie, F. E., Prudhomme, W. A., Magill, A. J., Forney, J. R., Permpanich, B., Lucas, C., Gasser, R. A., & Wongsrichanalai, C. (2005). White blood cell counts and malaria. *The Journal of Infectious Diseases, 192*(2), 323–330. https://doi.org/10.1086/431152

Morang'a, C. M., Amenga–Etego, L., Bah, S. Y., Appiah, V., Amuzu, D. S. Y., Amoako, N., Abugri, J., Oduro, A. R., Cunnington, A. J., Awandare, G. A., & Otto, T. D. (2020). Machine learning approaches classify clinical malaria outcomes based on haematological parameters. *BMC Medicine, 18*(2), 375-386. https://doi.org/10.1186/s12916-020-01823-3

Muppidi, P., Wright, E., Wassmer, S. C., & Gupta, H. (2023). Diagnosis of cerebral malaria: Tools to reduce *Plasmodium falciparum* associated mortality. *Frontiers in Cellular and Infection Microbiology, 13*(1), 389-401. https://doi.org/10.3389/fcimb.2023.1090013

Musa, F., Shaviya, N., Mambo, F., Abonyo, C., Barasa, E., Wafula, P., Sowayi, G., Barasa, M., & Were, T. (2021). Cytokine profiles in highly active antiretroviral treatment non-adherent, adherent and naive HIV-1 infected patients in Western Kenya. *African Health Sciences, 21*(4), 1584–1592. https://doi.org/10.4314/ahs.v21i4.12

Nader, E., Romana, M., & Connes, P. (2020). The red blood cell-inflammation vicious circle in sickle cell disease. *Frontiers in Immunology, 11*, 454. https://doi.org/10.3389/fimmu.2020.00454

Naing, C., Ni, H., Basavaraj, A. K., Aung, H. H., Tung, W. S., & Whittaker, M. A. (2024). Cytokine levels in the severity of *Plasmodium falciparum* malaria: An umbrella review. *Acta Tropica, 260*, 107447. https://doi.org/10.1016/j.actatropica.2024.107447

Obeagu, E. I. (2024). Role of cytokines in immunomodulation during malaria clearance. *Annals of Medicine and Surgery, 86*(5), 2873–2882. https://doi.org/10.1097/MS9.0000000000002019

Obeng-Aboagye, E., Frimpong, A., Amponsah, J. A., Danso, S. E., Owusu, E. D. A., & Ofori, M. F. (2023). Inflammatory cytokines as potential biomarkers for early diagnosis of severe malaria in children in Ghana. *Malaria Journal, 22*, 220. https://doi.org/10.1186/s12936-023-04652-w

Patel, H., Dunican, C., & Cunnington, A. J. (2020). Predictors of outcome in childhood *Plasmodium falciparum* malaria. *Virulence, 11*(1), 199–221. https://doi.org/10.1080/21505594.2020.1726570

Perkins, D. J., Were, T., Davenport, G. C., Kempaiah, P., Hittner, J. B., & Ong'echa, J. M. (2011). Severe malarial anemia: Innate immunity and pathogenesis. *International Journal of Biological Sciences, 7*(9), 1427–1442.

Shaviya, N., Budambula, V., Webale, M. K., & Were, T. (2016). Circulating interferon-gamma levels are associated with low body weight in newly diagnosed Kenyan non-substance using tuberculosis individuals. *Interdisciplinary Perspectives on Infectious Diseases, 7*(2), 364–375. https://doi.org/10.1155/2016/9415364

Song, X., Wei, W., Cheng, W., Zhu, H., Wang, W., Dong, H., & Li, J. (2022). Cerebral malaria induced by *Plasmodium falciparum*: Clinical features, pathogenesis, diagnosis, and treatment. *Frontiers in Cellular and Infection Microbiology, 12*(1), 532–544. https://www.frontiersin.org/articles/10.3389/fcimb.2022.939532

Sornsenee, P., Wilairatana, P., Kotepui, K. U., Masangkay, F. R., Romyasamit, C., & Kotepui, M. (2023). Relation between increased IL-10 levels and malaria severity: A systematic review and meta-analysis. *Tropical Medicine and Infectious Disease, 8*(1), 390–400. https://doi.org/10.3390/tropicalmed8010035

Trivedi, S., & Chakravarty, A. (2022). Neurological complications of malaria. *Current Neurology and Neuroscience Reports, 22*(8), 499–513. https://doi.org/10.1007/s11910-022-01214-6

White, N. J. (2018). Anaemia and malaria. *Malaria Journal, 17*(1), 371–380. https://doi.org/10.1186/s12936-018-2509-9

White, N. J. (2022). Severe malaria. *Malaria Journal, 21*(1), 284–292. https://doi.org/10.1186/s12936-022-04301-8

Wilairatana, P., Mala, W., Milanez, G. D. J., Masangkay, F. R., Kotepui, K. U., & Kotepui, M. (2022). Increased interleukin-6 levels associated with malaria infection and disease severity: A systematic review and meta-analysis. *Scientific Reports, 12*(1), 38–47. https://doi.org/10.1038/s41598-022-09848-9

Yamada, S., & Asakura, H. (2024). How we interpret thrombosis with thrombocytopenia syndrome? *International Journal of Molecular Sciences, 25*(9), 390–399. https://doi.org/10.3390/ijms25094956

Zekar, L., & Sharman, T. (2025). *Plasmodium falciparum* malaria. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK555962/