



Host-parasite biochemical reprogramming in malaria: clinical biochemistry, pathogenesis, and biomarker implications

Mohammad Sani Danboza^{1*}

¹Department of Biochemistry, Faculty of Science, Sa'adu Zungur University Bauchi, Gadau, Itas/Gadua, Bauchi State, Nigeria.

*Correspondence: mohammaddanboza@sazu.edu.ng; +2347030064452

Abstract	Article History
Severe malaria specifically caused by plasmodium falciparum infection is the leading cause of morbidity and mortality in endemic region like Nigeria. The severe malaria disease is characterized by excessive alterations in several biochemical parameters that demonstrate the Pathophysiological process behind the alterations. This review summarizes the integrated analysis of the mechanism underlying the major biochemical changes associated with plasmodium falciparum infection, including hemolysis-induced anemia (both intravascular and extravascular), hepatic injury and dysfunction, renal injury and impairment, metabolic abnormalities, electrolyte imbalance and hypoglycemia. These alterations are the byproducts of complex interaction between plasmodium falciparum and its human host arising from erythrocyte destruction, microvascular sequestration, tissue hypoxia and unregulated immune response. The review also highlighted in detail the observed biochemical derangement in severe malaria infection is amplified by oxidative stress and inflammatory cytokines which further contribute to multiple organ dysfunctions. Furthermore, routine biochemical markers such as serum lactate, bilirubin, creatinine and liver enzymes are analyzed for their clinical relevance in severity assessment, prognosis and therapeutic monitoring. Where available, clinically recognized thresholds and quantitative evidence linking biochemical abnormalities with diseases severity and mortality are considered to differentiate between established clinical markers and markers supported primarily by associative. Discovery of novel biomarkers with improved sensitivity for early detection of severity and risk stratification from recent finding in metabolomics and proteomic profiling were also analyzed in this review. Current scientific progress stress the need to integrate conventional clinical biochemistry analysis with genomics, proteomics, transcriptomics, metabolomics, clinical data, and artificial intelligence-based predictive models to enhance diagnostic precision and enable personalized disease management. Existing artificial intelligence applications in malaria, particularly automated parasite detection, classification, and emerging machine-learning approaches for clinical risk prediction were considered in relation to the potential production of multimodal severe-malaria prediction models. Such models could integrate routine biochemical biomarkers with multi-omics and clinical features to predicts clinically relevant outcomes, including severe malaria, acute kidney injury, cerebral involvement, metabolic acidosis, multi-organ dysfunction and mortality. Collectively, this approach represents a major avenue for future research with significant potential to transform clinical diagnosis, improved prognostic accuracy, enable individualized risk stratification and support targeted therapeutic intervention in severe malaria.	Received: 12/04/2025 Accepted: 05/07/2025 Published: 31/12/2025
	Keywords: Plasmodium falciparum; severe malaria; clinical biochemistry; biochemical markers; host–parasite interaction; oxidative stress; metabolic reprogramming; metabolomics; proteomics; multi-omics; artificial intelligence; biomarker discovery; prognostic biomarkers.
	License: CC BY 4.0*  Open Access Article
How to cite this paper: Danboza, M. S. (2025). Host-parasite biochemical reprogramming in malaria: clinical biochemistry, pathogenesis, and biomarker implications. <i>Gadua J Pure Alli Sci</i>, 4(2); 143 - 155. https://doi.org/10.54117/gjpas.v3i2.206	

Introduction

Malaria is an infectious disease caused by plasmodium infection, plasmodium is a single-celled protozoa and the common species of plasmodium associated with malaria in humans are plasmodium vivax, plasmodium falciparum, plasmodium malaria and plasmodium ovale, as a vector-borne disease, malaria is transmitted by infected female anopheles' mosquito when feeding on human blood. Amongst all four plasmodium species that cause malaria in humans, plasmodium falciparum remains the most dominant and deadliest species in Africa responsible for approximately 90% of malaria mortality every year (Merga, 2025) (Tandoh KZ, 2024). The intensity of plasmodium infection is determined by several factors including the nature of the parasite itself (species), the vector (life span, strong biting habit), the human host (immunity) and the environment (climatic condition) ((CDC), 2024) (World Health Organization, 2024).

The infecting species of plasmodium associated with malaria determined the clinical severity of the disease. Malaria normally presents as an acute febrile disease having an incubation period of at least 7 days. Hence fever that occurs below seven days of initial exposure is likely to be another disease than malaria ((CDC), 2024). The most severe cases of malaria manifestations are associated with plasmodium falciparum infection. It presents diverse clinical features that include fever (often periodic), sweating, headache, muscle pain, joint pain, loss of appetite, chill, vomiting, muscle weakness, diarrhea, mild cough, dizziness and abdominal discomfort ((CDC), 2024). Advanced complication involving multiple organs dysfunction may arise, including acute kidney injury, widespread seizure, pulmonary edema, metabolic abnormalities, and hematological manifestations, that may progress into coma and ultimately death (World Health Organization. Malaria, 2025). Physical manifestations of malaria include elevated body temperature, pallor (due to anemia), mild jaundice, hepatomegaly, splenomegaly and tachycardia ((CDC), 2024) (Okello, 2026).

Methodology

The review was conducted using a structured and comprehensive literature search to evaluate current evidence on severe plasmodium falciparum malaria with emphasis on emerging biomarkers and pathophysiology, particularly metabolomics, proteomics, genomics, oxidative stress markers, inflammatory cytokines and AI-based predictive approach. A systemic search of existing publications was performed using electronic databases PubMed/MEDLINE, Scopus, Google Scholar, Web of Science, Embase, and ScienceDirect. The literature search covered studies published between January

2015 and June 2026 to ensure that most recent advances in malaria research were included, while landmark studies published before 2015 were retained where necessary to explain the fundamental mechanisms of malaria pathogenesis, erythrocyte invasion, cytoadherence, and host-parasite interactions.

Studies were considered eligible if they investigated severe *P. falciparum* malaria and reported biochemical, hematological, metabolic, immunological, metabolomic, proteomic, genomic, or oxidative stress biomarkers associated with disease pathogenesis, diagnosis, prognosis, or therapeutic monitoring. Selected publications included systemic review, randomized clinical trials, meta-analysis, observational studies, prospective and retrospective cohort studies, case control studies, and high quality experimental investigations published in peer-reviewed journals.

The review was conducted in accordance with the principle outlined in the PRISMA 2020 statement for reporting systemic review and was informed by recommendations from the Cochrane Handbook for systemic Reviews of interventions to enhance methodological transparency and reproducibility. In addition, internationally recognized data resources, including World Health Organization (WHO), Center for Disease Control and Prevention (CDC) were consulted where appropriate to identify emerging evidences.

Synthesis and integrative framework

This review applied a structured evidence-synthesis framework based on four interconnected domains: (1) initiating host-parasite process (2) biochemical alteration (3) pathophysiological consequences (4) clinical outcomes to systematically integrate the heterogeneous biochemical findings reported across studies on severe malaria. Evidences were selected according to the precision of finding across the existing literatures, biological plausibility, and clinical validation of the individual biomarkers.

First domain represents the initiation process of *P. falciparum* infection (erythrocyte invasion, parasite sequestration, hemoglobin digestion, tissue hypoxia, altered parasite and host metabolism, activation of innate and active immune response) that serve as the biological drivers for the biochemical disturbances.

Second domain comprises of measurable biochemical alterations such as blood glucose, lactate, cytokines, hematological, liver and kidney parameters.

Third domain links biochemical abnormalities to pathophysiological mechanism like erythrocyte destruction, microvascular sequestration, lactate accumulation.

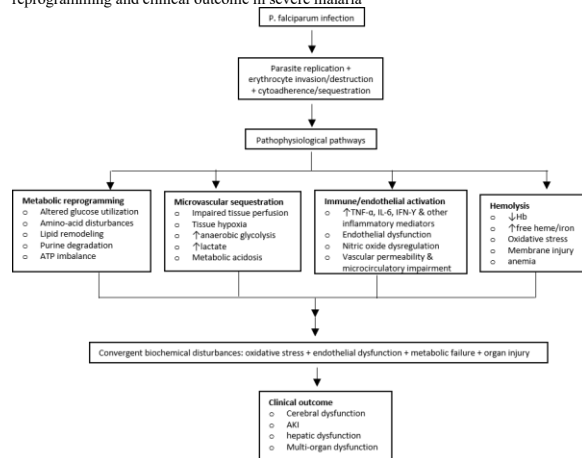
Fourth domain considers clinically relevant outcome such as metabolic acidosis, AKI, hepatic dysfunction. The biomarkers were interpreted according to whether they represent a mechanistic marker, severity marker, organ-injury marker or prognostic marker.

To distinguished already established clinical indicator from emerging biomarkers the evidence was categorized into four levels:

Level I: clinically established evidences supported by recognized clinical or WHO-defined threshold

Level II; quantitative prognostic or associative evidences

Figure1; integrated framework linking host-parasite interactions to biochemical reprogramming and clinical outcome in severe malaria



Malaria Burden in Nigeria and sub-Sahara Africa

Malaria remain overwhelmingly concentrated in Africa as highlighted by the recent world health organization report and Nigeria is at the epicenter of the global burden. WHO reported in 2023 that approximately 263 million malaria cases is recorded worldwide (95% CI: 238 - 294 million) corresponding to an incidence of 60.4 cases per 1000 people at risk, an increase from 58.6 per 1000 in 2022. About 94% of this malaria cases occur in Africa underscoring the persistent vulnerability of sub-Saharan Africa. Within this framework, a significant proportion of malaria is concentrated in few high transmission countries notably Nigeria, Democratic Republic of Congo, Uganda, Ethiopia, and Mozambique, which together constitute half of the global malaria incidence. However, Nigeria particularly bears the heaviest burden considering the size of its population, high intensity of transmission and malaria control challenges (World Health Organization., 2024).

In 2023 the estimated global deaths due to malaria is recorded at 597,000, about 95% of which occurs in the WHO African region. The global mortality rate stood at 13.5 deaths per 100,000 populations, standing significant above the reduction target set by Global Technical Strategy for Malaria (2016 - 2030) which

stand at 9.8 per 100,000 populations in 2020 after falling from 14.9 per 100,000 populations in 2015 indicating clear deviation from trajectory required to achieve 90% reduction by 2030. Disturbingly more than half of malaria associated mortality were concentrated in just four countries: Nigeria, Democratic Republic of Congo, Niger and Tanzania (World Health Organization., 2024).

The severe malaria outcome and high mortality rate recorded in Nigeria is likely as a result of persistent high transmission intensity, compounded by poor health care system, untimely diagnosis and ineffective treatment protocol, coupled with emerging vector and parasite resistance. Complications brought about by severe malaria such as cerebral malaria, metabolic acidosis, severe anemia, and multiple organ dysfunction is the major cause of mortality particularly among pregnant women and children in Nigeria. The recent increase in global mortality rate from 9.8 to 13.9 per 100,000 populations therefore demonstrate not only systemic gaps in malaria control but the need to improve clinical management and leverage accurate and sensitive diagnostic and prognostic tools, like clinical biochemistry markers to enable early detection of malaria severity and improve patients outcome in Nigeria and similar endemic settings (World Health Organization. Malaria, 2025)

The review focuses on exploring the clinical biochemical alteration that is brought about by severe malaria, emphasizing both on the mechanism underlining the clinical alterations and their relevance in diagnosis and management of the disease. Severe malaria particularly caused by plasmodium falciparum is characterized by several organ-specific and metabolic disturbances cause by the parasite proliferation, hemolysis and unregulated host immune response.

The complex interaction between parasite metabolism and host Pathophysiology lead to significant biochemical abnormalities such as hypoglycemia, lactic acidosis, electrolyte imbalance, hepatic dysfunction, oxidative stress, acute renal injury, impaired tissue perfusion, and inflammatory cytokines release. Understanding the biochemical mechanism behind these pathways provide insight into how systemic complications of severe malaria such as severe anemia, cerebral malaria and multi organ failure develop (Okagu, 2022).

The clinical biochemical markers selected in this review serve not only as indicators of malaria severity but also as tools for early diagnosis, risk assessment and therapeutic monitoring critical for accurate and precise clinical decision-making.

Pathophysiology of malaria

Life cycle of *P. falciparum*

vector

Gut: *Plasmodium* parasite have evolved a highly intricate life cycle using mosquito as a transmission vector to infect its host. When female anopheles' mosquito bite and ingest blood from host containing the sexual form of parasite (gametocyte) circulating in an infected person blood stream. The gametocyte matures into both male and female gametes in the midgut of the infected mosquito. The differentiated male and female gamete fertilize to form zygote; the zygote will further differentiate into motile ookinete. The motile ookinete penetrate the gut wall, round up and develop into oocysts at the outer surface forming a protective capsule that anchors to the gut wall serving as site of multiplication. The oocysts grow and release thousands of sporozoites. **Salivary gland:** sporozoites traveled to the mosquito salivary gland making it infectious (van Schuijlenburg, 2024) (Tan, 2021).

Human Host

Hepatic Stage: After infectious mosquito bite, sporozoites present in the mosquito is introduced into the human host, the sporozoites leave the bite site and find their way to the liver through a complex and perilous journey (Risco-Castillo, 2013). The sporozoites cross liver sinusoidal wall into the hepatocyte with the aid of surface protein interaction on both sporozoites (circumsporozoite protein (CSP)) and hepatocyte (Highly Sulfated Heparan Sulfate Proteoglycan (HSPGs)), enabling the parasite to distinguish hepatocyte from other cells in the liver. After selective attachment of sporozoites to hepatocyte, the sporozoites enters the hepatocyte through active invasion and get invaginated by the hepatocyte cell membrane forming parasitophorous vacuole aim at evading host immune attack and preventing lysosomal destruction. Within this protective niche, the sporozoites differentiate into liver schizont producing thousands of merozoites. Hence hepatocyte invasion and parasitophorous vacuole formation are critical events in malaria pathogenesis constituting target for pre-erythrocytic therapy and vaccine design (Risco-Castillo, 2013) (Vaughan, 2017) (Centers for Disease Control and Prevention, 2024).

Erythrocytic stage

Entry of merozoites: This stage begins with the rupture of hepatocyte after full maturation of liver schizont releasing thousands of merozoites into the blood stream. The circulating merozoites recognize a specific surface protein on red blood cell attached itself enabling it to invade the erythrocyte forming

parasitophorous vacuole inside the RBC. Intra-erythrocytic development: once inside RBC *plasmodium falciparum* undergoes different morphological transformation (Alam, 2026) (Cowman, 2017).

Ring stage (early trophozoites): it is the earliest intra-erythrocytic development stage of *plasmodium falciparum*, appears as thin cytoplasmic ring with one or two chromatin dots and a central vacuole under light microscope. Multiple ring forms may be present on single red blood cell indicating *p. falciparum* infection (Alves-Rosa, 2024). The parasite is metabolically active at this stage although they may appear small, they initiate the digestion of hemoglobin activating essential biosynthetic pathways and modification of host erythrocyte membrane require by the parasite for growth and development. As the parasite continues to grow and develop into trophozoites. At this stage the parasite start producing a protein that contribute to cytoadherence and sequestration (Alves-Rosa, 2024) (Cowman, 2017).

Trophozoites stage: during this stage in *P. falciparum* infection the parasite undergoes rapid growth and became highly active metabolically synthesizing protein, replicating nucleic acid and membrane within the host erythrocyte leading enlargement of the host cell. The nutrient require for this intensive metabolic activity is derived from large scale digestion of hemoglobin inside a specialized digestive vacuole releasing Ferriprotophyrin IX (free heme) as by product. Ferriprotophyrin IX generate oxidative stress that can damage cell membrane making it toxic to the parasite, the parasite converts it into nontoxic insoluble crystalline pigment called haemozoin that accumulate within the trophozoites giving the infected RBC a characteristic dark granular appearance under microscope. This is an important diagnostic feature of *P. falciparum* infection (Wiser, 2024) (Gupta, 2022).

Schizonts stage: This is the most mature and final intracellular stage of erythrocytic stage of *plasmodium falciparum*, it responsible for rapid multiplication of *plasmodium falciparum* that drive severe malaria. After trophozoites become metabolically active, the nucleus divides into multiple nuclei without immediate cell division. This results in occupation of the entire cytoplasm of the host erythrocyte by the parasite material (Alam, 2026). The parasite cytoplasm begins to segment around each nucleus forming multiple daughter cell within the host erythrocyte. The stage is called schizont (from the tern "schizogony" meaning multiple fission). after fission each segment develop into invasive form called merozoites that can infect new RBC. Each schizont can produce 16 - 32 merozoites making this stage

critical for *P. falciparum* amplification in the blood stream. Fully mature schizont rupture the infected RBC releasing the newly form merozoites into the blood stream initiating new cycle of erythrocytic infection. This stage trigger most of the clinical symptoms of malaria such as fever spike due to parasite antigen, haemozoin pigment and inflammatory molecules are suddenly release into the blood circulation (Alam, 2026) (Cowman, 2017) (World Health Organization, 2024).

Microvascular sequestration

Under normal condition old, damage or infected red blood cell are remove from circulation the spleen through extravascular hemolysis, plasmodium falciparum as it develop from ring to trophozoites and schizont state within an infected RBC it produce a surface protein called Plasmodium Falciparum Erythrocyte Membrane Protein 1 (PfEMP1) expressed on the knob-like structure on the infected erythrocyte (Wiser, 2023). PfEMP1 interact with surface receptors such as CD36, Thrombospondin, ICAM-1, Endothelial protein C Receptor (EPCR), Oncofetal Chondroitin Sulfate, ABO Blood group Antigen VCAM, E-selectin, and chondroitin-4-sulfate (Jensen, 2020) enabling it to stick to the blood vessel wall a process called cytoadherence avoiding extravascular destruction by the spleen. When many infected RBC adhere to the blood vessels wall at the same time the capillaries become partially block causing reduced blood flow, tissue hypoxia and subsequently local ischemia (Gill, 2023) (Othman, 2023). The infected RBC also bind with health RBC (Rosetting) and platelet (Clumping) thereby increasing the size of the blockage worsening tissue damage downstream (Bernabeu, 2017) (Bachmann, 2022).

Tissue hypoxia brought about by microvascular sequestration downstream of the microvascular blockage results in several biochemical alterations such as Cellular oxygen deprivation; this is experienced by tissues that rely on continuous oxygen supply, once the oxygen supply is deficient the tissue can no longer depend on usual aerobic respiration in the mitochondria. To survive the tissue switch to anaerobic metabolic process that allow limited ATP generation in the absence of oxygen producing lactic acid as a metabolic byproduct (Ohiagu, 2021). Accumulation of lactic acid from this survival strategy lead to lactic acidosis a major contributor to metabolic acidosis associated with severe malaria (Ohiagu, 2021). To correct the metabolic acidosis associated with tissue hypoxia, the body try to compensate by increasing the rate of oxygen intake through rapid breathing. Lactic acidosis provide correlation between parasite sequestration and metabolic derangement

observed in severe malaria (Ohiagu, 2021) (. Lendongo Wombo, 2023) (Pikor, 2025).

Immune activation

Immune attack in plasmodium falciparum is both complex and high in erythrocytic stage than pre-erythrocytic stage of the parasite. The major immune players are CD8+ and antibodies. The first immune attack on plasmodium falciparum begin at a point of inoculation of sporozoite into the skin by the vector. The sporozoite stay in the skin for several hours after inoculation before they gets activated for hepatic journey. 50% of the inoculated sporozoite could not leave the infection site as they attack by antibodies present in the skin tissue. Hence, this early stage provide a critical target for vaccine design (Frischknecht, 2017)

After invasion of the bloodstream by *P. falciparum*, the infected RBC and molecules derived from parasite metabolic activities such haemozoin and and glycosylphosphatidylinositol (GPI) anchors are recognized by phagocytic immune cells like macrophages, dendritic cells and monocyte which triggers strong inflammatory response aim at limiting replication of the parasite (Segbefia, 2024). On the order hand excessive activation of the inflammatory immune response contribute significantly to the development of severe malaria. This is because release inflammatory cytokines triggers the expression of more adhesion molecules by endothelial cells making blood vessel more sticky to the infecting RBC promoting microvascular sequestration, which subsequently lead to hypoxia and tissue damage (Sakoguchi, 2022). Further, excessive immune activation promote production of nitric oxide and reactive oxygen specie (such as super-oxide anion $O_2^{\cdot -}$, hydrogen peroxide H_2O_2 , Hydroxyl radical $OH^{\cdot}$, Singlet oxygen $^1O_2$), although help kill the parasite in large number they also damage endothelial cell, erythrocyte and the surrounding tissue contributing to inflammation, hemolysis and tissue damage (key feature of severe malaria).

Major Biochemical Alteration

Hemolysis and anemia

ANEMIA is an important clinical manifestation of severe malaria that is define as a clinical condition in which hemoglobin (Hb) level is below the normal range. Malaria infection contribute to anemia through three different mechanisms: Intravascular hemolysis brought about by parasite and inflammatory activities, extravascular hemolysis through direct removal of infected RBC in liver, spleen and bone marrow, and Reduced RBC production by dysregulated erythropoiesis (White, 2018).

Severe anemia is responsible for greater percentage of malaria associated mortality, this is because reduce hemoglobin level promote nutritional deficiency, poor health structure and enable prevalence of other infectious disease like viral, bacteria and intestinal helminth infection (hookworm) (White, 2018) (White, 2022).

Red blood cell is constant destroyed during malaria infection as a result different biochemical and physiological activities of both the parasite and its human host. Some of the parasite activities that contribute hemolysis include: During the life cycle of *p. falciparum* the infected Red Blood Cell get ruptured after the schizont stage to release mature merozoites that start new cycle of erythrocytic infection. (Okagu, 2022). Large amount hemoglobin derived product as well as free hemoglobin, Heamin (ferric haem), methemoglobin (MetHb), degraded hemoglobin peptide, and hemozoin are release into the circulation when an infected red blood cell rupture after schizogony completion by the parasite. These molecules are highly reactive contributing directly to further destruction of red blood cell, by generating ROS, and initiating of inflammatory response thereby increasing hemolysis (intravascular hemolysis) several-fold. (Moxon, 2020). Furthermore, destruction of iRBC occur in the liver, spleen and bone marrow (extravascular hemolysis) with help of phagocytic cells. This is triggered by change in cell deformability and expression of some surface molecules such as phosphatidylserine (PS) and Rhoptry Associated protein-2 (RSP-2) (Moxon, 2020) (Bissinger, 2024). It is also observed that erythropoiesis is disrupted in severe malaria infection through different process including: release of inflammatory cytokines trigger by plasmodium infection is established to stimulate the release of Hepcidin in the liver. Hepcidin is a hormone that control iron storage and absorption. This result in delocalization leading to hypoferremia, and subsequent disruption of erythropoiesis in the bone marrow (Ganz, 2012).

Heamin induce reduction of cytokines RANTES is also discovered to interfere with erythropoiesis in malaria infection. Dysregulation of innate inflammatory mediators as a result of haemozoin initiate phagocytosis by macrophages and monocyte inhibit erythroid development leading to reduced reticulocyte response. Macrophages Migration Inhibitory Factor (MIF) released by macrophages after iRBC and haemozoin phagocytosis are believe to poses bone marrow suppression activity and inhibit the formation of erythropoietin-dependent erythroid colony. These three mechanism: intravascular hemolysis, reduced RBC production and extravascular hemolysis contribute significantly to severe anemia associated with malaria. (Deroost, 2016).

Table 1 Hematological parameters affected in malaria

parameter	Reference range	Severe malaria threshold	Extravascular hemolysis (splenic clearance)	Intravascular hemolysis (RBC rupture in blood)	Reduced erythropoietic production
Hemoglobin (Hb)	Adult male: 13-17g/dl, female: 12-16 g/dl	No validated threshold	Decrease due to macrophage removal of RBC	Decrease due to direct RBC destruction	Decrease due to inadequate production of new RBC (Glatt, 2025)
Packed cell volume (hematocrit)(PCV)	36 – 52% (Karita, 2009)	No validated threshold	Decrease due to gradual reduction of RBC	Decrease due to sudden hemolysis	Decrease due to decrease RBC formation (Glatt, 2025)
RBC count	Male: 4.5-5.9x10 ¹² /L, Female: 4.0-5.2x10 ¹² /L (Karita, 2009)	No validated threshold	Reduce due to clearing of damaged RBC by the spleen	Reduce due to rupture of RBC	Reduce due to suppressed bone marrow production (Glatt, 2025)
Reticulocyte count	0.5 – 2.5% (Karita, 2009)	No validated threshold	Increase as the bone marrow tries to compensate	May increase if the bone marrow is still responsive	Decrease due to suppress erythropoiesis (dyserythropoiesis) (Liu, 2025)
Mean corpuscular volume (MCV)	80 – 100 fL (Karita, 2009)	No validated threshold	Slight increase due to increase reticulocyte	Slight increase due to reticulocytosis	Decreases or remain normal depending on nutritional deficiency or bone marrow suppression (Liu, 2025)
Mean corpuscular haemoglobin	27-33pg (Karita, 2009)	No validated threshold	normal	normal	Decreases if erythropoiesis is impaired or iron metabolism is altered (Liu, 2025)
Mean corpuscular haemoglobin concentration (MCHC)	32-36 g/dL (Karita, 2009)	No validated threshold	normal	normal	may decrease if defective RBC production occur (Liu, 2025)
Platelet count	150-450x10 ⁹ /L (Karita, 2009)	No validated threshold	Decreases due to splenic sequestration	Decreases due to systemic destruction	May be normal or decrease due to bone marrow suppression (Liu, 2025)
White blood cell count	4 – 11 X 10 ⁹ /L (Karita, 2009)	No validated threshold	Normal or slightly decrease	Normal or slightly decrease	Decrease if bone marrow suppression become severe (Liu, 2025)

The hematological alteration shown in table1 is supported by recent studies demonstrating that severe plasmodium falciparum infection lead to both hemolysis and dyserythropoiesis responsible for reduce hemoglobin, RBC count, hematocrit along with abnormal reticulocyte responses and red-cell indices (Glatt, 2025) (Liu, 2025) (Gupta, 2025) (Carret, 2025).

Alteration in Liver Function Parameters

One of the common biochemical complication associated with plasmodium falciparum infection is liver dysfunction reflecting hepatocellular injury cause by both hepatic and erythrocytic stage of the parasite development (Alves-Rosa, 2024). After inoculation of the parasite by the vector, sporozoites rapidly migrate to the liver and invade hepatocyte, the parasite undergoes intracellular differentiation and multiplication into mature liver schizont which then rupture the infected hepatocyte membrane and release its content into blood circulation (liver enzymes). the rupture of hepatocyte and subsequent inflammatory response contribute to further hepatic injury. This lead to increase in liver enzymes (Alanine Amino Transferase ALT and Aspartate Amino Transferase (AST) in the blood stream indicating hepatocellular injury (Chughlay, 2020). Furthermore, massive destruction of RBC (infected and uninfected) during erythrocytic stage of the parasite development increase the rate of production of bilirubin. However, the liver is no longer at its full capacity to conjugate the produced bilirubin due to injury mentioned. This result in hyperbilirubinemia an important parameter for liver damage. Other liver parameters affected are alkaline phosphatase (ALP), Gamma-glutamyl Transferase (GGT), albumin, and Prothrombin time (PT) (Derwesh SA, 2025).

Table 2 Liver parameters in malaria infection				
Parameter	Reference range	Findings in malaria infection	Severe malaria threshold	pathophysiology
AST	10 – 40U/L	Elevated	No universal cutoff	Hepatocellular injury and enzyme leakage (Derwesh SA, 2025)
ALT	7 – 56U/L	Elevated	No universal cutoff	Direct liver injury during hepatic state (Chughlay, 2020)
Total bilirubin	0.3 – 1.2 mg/dL	Elevated	>3 mg/dL with high parasitemia under WHO criteria	Massive hemolysis and impaired liver conjugation capacity (Chughlay, 2020)
Direct bilirubin	0-0.35 mg/dL	Elevated in (severe case)	No universal cutoff	Hepatic dysfunction and cholestasis (Chughlay, 2020)
Indirect bilirubin	0.2-0.8 mg/dL	Elevated	No universal cutoff	Excessive hemolysis during erythrocytic stage (Chughlay, 2020)
ALP	44-147U/L	Mild-moderate increase	No universal cutoff	Hepatic inflammation and cholestasis (Chughlay, 2020)
GGT	9 – 48U/L	Elevated in some cases	No universal cutoff	Oxidative stress and hepatocellular injury (Chughlay, 2020) (Siddig AM, 2026)
Albumin	3.5 – 5.0g/dL	reduced	No universal cutoff	Impaired liver synthetic capability (Siddig AM, 2026)
Prothrombin time (PT)	9.4 – 12.5 seconds	Prolonged	No universal cutoff	Impaired liver synthetic capability (Siddig AM, 2026)

The changes in liver parameters presented in the table demonstrate multi-factorial hepatic involvement that take place during plasmodium falciparum infection leading to hepatic injury as indicated by elevated level of AST and ALT, prolonged PT and reduce albumin concentration indicating reduce liver synthetic capacity, marked increased in direct and indirect bilirubin demonstrate massive hemolysis and reduced hepatic function, while mild increase in ALP and GGT support cholestatic. These biochemical abnormalities together constitute an evidence that liver dysfunction in malaria is not solely a consequence of massive hemolysis but also a direct effect of parasite-induced hepatocyte injury and inflammatory damage that increases with increase in parasite density and disease severity (Chughlay, 2020) (Derwesh SA, 2025) (Siddig AM, 2026) (Prenen, 2025).

Alteration in Renal Function Parameters

Reduced kidney function is observed in severe plasmodium falciparum infection demonstrated by increase concentration of serum creatinine and blood urea. These two parameters a important kidney function markers reflecting reduced glomerular filtration rate (GFR) and impaired renal clearance of metabolic byproduct (Meena, 2026). The reduce renal function recorded in severe malaria is contributed by kidney damage due several mechanisms including: Intravascular hemolysis causing the release of large amount of hemoglobin into the circulation. The free hemoglobin released by intravascular hemolysis gets accumulated in the renal tubule leading tubular obstruction and direct oxidative injury to renal cells (Meena, 2026) (Oluwatuyi KO, 2024). Microvascular sequestration: infected erythrocyte sticks to the blood vessel wall reducing blood flow to the kidney leading to tissue hypoxia and ischemic injury. Furthermore, the intense inflammatory response triggered by severe plasmodium infection result in cytokine release and oxidative stress that further damage kidney tissue (Basire, 2025) (Kazing, 2025). Biochemically this damage appears as elevated serum creatinine and blood urea level, therefore early detection is essential

for identifying at-risk patient guiding fluid management and supportive therapy (renal monitoring and dialysis

Table 3: Kidney parameters and their associate with malaria					
parameter	Change in malaria	Reference range	Severe malaria threshold	Mechanism responsible	Clinical implication
Serum creatinine	elevated	0.6 – 1.3 mg/dL in adult	>3mg/dL	Reduced GFR, Hb induced tubular injury, and microvascular sequestration	Acute kidney injury (AKI) in severe malaria
Blood urea (BUN)	Elevated	2.5 – 7.1 mmol/L	>20 mmol/L	Reduced renal clearance of nitrogenous waste and decreased renal perfusion	Demonstrate impaired renal excretory function and progression toward renal failure
Serum cystatin C	Elevated	0.6-1.0 mg/dL	No validated threshold	Early decline in kidney filtration prior to creatinine rise	Early marker for AKI in severe malaria especially in children
Urine output	Decreases (oliguria/anuria)		No validated threshold	Acute tubular necrosis cause by hemolysis, inflammation and ischemia	Indicate severe renal involvement and poor prognosis
Electrolyte (K ⁺ , Na ⁺)	Abnormal (increase K ⁺)	Na ⁺ : 135-145mmol/L K ⁺ : 3.5-5.0mmol/L	No validated threshold	Impaired tubular function and reduced filtration	May lead to hyperkalemia (life threatening complication)
Urinary protein	Elevated		No validated threshold	Glomerular and tubular damage	Indicate structural kidney damage in severe malaria
Hemoglobinuria	present		No validated threshold	Massive intravascular hemolysis	Malaria related acute kidney injury

Alteration of major kidney biochemical in severe plasmodium falciparum infection is presented in the table indicating elevated level of serum creatinine and blood urea with reduced urine and electrolyte imbalance, this reflect progressive impairment of kidney function as a result of microvascular sequestration of iRBC, excessive intravascular hemolysis and renal hypo-perfusion. This alteration plays an important role in early detection and clinical monitoring of acute kidney injury (AKI) in malaria (Meena, 2026) (Oluwatuyi KO, 2024) (Basire, 2025) (Kazing, 2025).

Metabolic alteration

Severe malaria is associate with several metabolic abnormalities, as a result of reduced oxygen supply to the tissue, this is brought about by microvascular sequestration and hemolytic anemia (as result of both intravascular and extravascular hemolysis). because of reduced oxygen supply to the tissue, cell is forced to shift from aerobic to anaerobic metabolism where glucose is channel to lactic acid production instead of production of pyruvate by glycolysis (van Niekerk, 2023). The excessive production of lactate from glucose to meet the energy demand of the tissue in limited oxygen supply result in metabolic acidosis. Accumulation of lactate lead fall in physiological pH (Possemiers, 2021). FEAST analysis included 1,719 children with *P. falciparum* and found that ≥40% lactate clearance or normalization below 2.5mmol/L at 8 h was associated with survival while, clearance of ≥10% was associated significantly with higher morality (Aramburo A, 2018). Furthermore, another common metabolic alteration observed in severe malaria infection is hypoglycemia, this occur due to increase blood glucose consumption by the parasite (which rely heavily on glucose energy), the consumption glucose increased with increased parasite density. The parasite rely heavily on glycolysis for energy generation because it lacks fully

functional oxidative phosphorylation pathway, experimental metabolic modelling studies have demonstrate that glycolytic rate of an infected erythrocytes dramatically increases by up to nearly hundred fold causing rapid uptake of glucose from the bloodstream (van Niekerk, 2023). the combination of parasite glucose consumption, increased host tissue glucose utilization due to fever, inflammation, and immune action result in depleted blood glucose in patient with severe malaria infection (Prenen, 2025) Metabolic acidosis and hypoglycemia together constitute an importing biochemical markers for management of severe malaria.

Table 4: Metabolic parameters and their clinical relevance in severe malaria

Parameter	observe changes	Reference range	Severe malaria threshold	pathophysiological mechanism	clinical significance
blood lactate	elevated	0.5 – 2.2 mmol/L	≥5 mmol/L	tissue hypoxia and parasite derived lactate production	indicator of metabolic acidosis
blood pH/bicarbonate	decreased	22-29mmol/L	<15 mmol/L	excess lactate accumulation and impaired lactate clearance (liver and kidney dysfunction)	confirm metabolic acidosis and severe infection
blood glucose	decreased	3.9 – 5.5 mmol/L	<2.2mmol/L	increase parasite glucose consumption, host metabolic demand and quinine induced hyperinsulinemia	major complication associated with neurological symptoms and poor prognosis
Lactate clearance	reduced	Not a conventional normal range	≥40% decline and/or <2.5 mmol/L associated with better survival	impaired hepatic gluconeogenesis and kidney dysfunction	contribute to persistent hypoglycemia in severe malaria

The alterations in the metabolic parameter demonstrated in table highlighted the central role of metabolic acidosis and glucose dysregulation in Pathophysiology of severe malaria. Hypoglycemia and elevated blood lactate are interconnected consequences of parasite metabolism and altered host metabolic regulation. In addition, contemporary research on antimicrobial pharmacology demonstrated that quinine can directly stimulate insulin secretion aggravating hypoglycemia during treatment of severe malaria (Lu, 2025).

Oxidative stress and inflammation

Oxidative stress originates from multiple source during malaria infection including parasite-mediated hemoglobin digestion, intravascular hemolysis, and immune cell activation. The parasite-mediated digestion of hemoglobin release free heme and iron that catalyze the formation highly active free radicals through Fenton reaction (Gomes, 2022). Activated immune cells such as neutrophils and macrophages produces reactive oxygen species (ROS) as part of inflammatory response strategy designed to destroy the parasites. However, excessive release of ROS contributes significantly to host tissue damage and severe of the disease (Gomes, 2022). these plays critical roles Pathophysiology of malaria especially when rate of production of ROS exceeds the capacity of host antioxidant defense system. Recent studies confirm that oxidative stress is the key mechanism responsible for anemia, liver dysfunction and cerebral malaria supporting the concept that oxidative stress is a major driver of pathogenesis of malaria rather than

just a secondary consequences of infection (Gomes, 2022).

Table 5: Oxidative stress parameter and their alteration in malaria infection

Parameter	Type	Alteration	Reference range	Severe malaria threshold	Pathophysiological Significance
Reactive oxygen specie (ROS)	Pro-oxidant marker	increased	Assay dependent	None established	Generated from Hb digestion, immune cell activation and inflammatory response (Gomes, 2022)
Melalndialdehyde (MDA)	Lipid peroxidation marker	increased	1-2 umol/L	None established	Indicate oxidative damage of RBC membrane and tissue (Gomes, 2022)
Superoxide dismutase (SOD)	Antioxidant enzymes	Decreased	Assay dependent	None established	Reduced antioxidant defense against superoxide radicals (Kotepui, 2024)
Reduced glutathione (GSH)	Non-enzymatic antioxidant	Decreased	Assay dependent	None established	Depletion due neutralization of excess free radical (Kotepui, 2023)
Glutathione peroxidase (GPx)	Antioxidant enzyme	Decreased	Assay dependent	None established	Reduced ability to detoxify H2O2 and lipid peroxides (Kotepui, 2023)
Catalase (CAT)	Antioxidant enzymes	Decreased	Assay dependent	None established	Reduced breakdown H2O2 and increased oxidative damage (Gomes, 2022)
Lipid peroxidation (general)	Oxidative damage marker	increased	Assay dependent	None established	Lead to membrane instability and hemolysis (Gomes, 2022)
Total antioxidant capacity (TAC)	Overall antioxidant status	Decreased	Assay dependent	None established	Reflects imbalance between oxidants and antioxidants (Gomes, 2022)

The table demonstrate alteration in oxidative stress parameters in malaria infection. Characteristic increase in ROS, and lipid peroxidation markers such as MDA, along with significant decrease in antioxidant defence like SOD, GSH, CAT and GPx.

Metabolomics

Recent development in clinical biochemistry have shifted malaria research from conventional biomarkers such as liver enzymes, Hb, creatinine and bilirubin to emerging biochemical markers that better reflect immune dysregulation, disease severity and metabolic failure. The emerging biochemical markers include metabolomics signature, inflammatory cytokines and blood lactate, these three markers are increasingly recognized as powerful tools for prognosis and early identification of severe malaria. Metabolomics provide the global view of metabolic disturbance associated with plasmodium falciparum infection by detecting hundreds metabolite simultaneously instead of measuring a single biochemical parameter enabling early detection of tissue dysfunction and disease severity.

Multi-omics study conducted in 2025 demonstrated that distinct metabolic signature is observed in children with severe malaria infection, this signature include characteristic alteration in lipid metabolism, reduced arginine metabolites, and increase in stress-related metabolite such as pipecolic acid and cortisol (Sobota, 2025). similarly, another study conducted in 2024 demonstrates significant disruption in metabolism of amino acids, vitamin B6, fatty acid and oxidative stress metabolites in plasmodium vivax infection (Yakubu, 2024). furthermore, it is also established that malaria alter host glucose metabolism, lactate production and purine metabolism (Cobbold, 2016).

Cytokines

Cytokines plays critical role in malaria Pathophysiology, by reflecting the host inflammatory response hence serve as an important biochemical marker. As remonstrated by recent advances in multi-omics research shows that severe malaria shares similar inflammatory signatures such as up-regulation of several mediators linked to cytokines activities. These inflammatory biomarkers were strongly linked to severe clinical manifestation like severe anemia and cerebral malaria (Sobota, 2025).

Table 6: Oxidative stress parameter and their alteration in malaria infection						
category	Biochemical marker	Reference range	Severe malaria threshold	Alteration	Underlying mechanism	Clinical significance
Glucose metabolism	Blood glucose	3.9 – 5.5 mmol/L	<2.2 mmol/L	Decrease	Increase glucose consumption by the parasite and reduce hepatic gluconeogenesis	Hypoglycemia associated with coma, seizures and severe malaria (Li, 2025)
Lactate metabolism	Blood lactate	0.5 – 2.2 mmol/L	≥5 mmol/L	Increased	Tissue hypoxia, anaerobic glycolysis and parasite metabolism	Indicate metabolic acidosis (strong prognostic marker) (Ishika, 2024)
Energy metabolism	pyruvate	0.03-0.10 mmol/L	No validated cutoff established	Increased	Accelerated glycolysis due to hypoxia	Indicates impaired oxidative metabolism (Mbuli, 2025)
	ATP production		No validated cutoff established	Decreased	Mitochondrial dysfunction and tissue hypoxia	Lead to organ failure in severe malaria (Mbuli, 2025)
Amino acid metabolism	Arginine	50-150 umol/L	No validated cutoff established	Decreased	Reduced nitric oxide synthesis and endothelial dysfunction	Promote microvascular damage and severe malaria (Sobota, 2025)
	Phenylalanine	35-85 umol/L	No validated cutoff established	Increased	Impaired liver function and alteration of amino acid metabolism	Associated with severity of malaria (Mbuli, 2025)
	Tryptophan	40-90 umol/L	No validated cutoff established	Decreased	Immune-mediated metabolism through indoleamine pathway	Reflects immune activation and inflammation (Sobota, 2025)
Lipid metabolism	lysophosphatidylcholines (LPCs)		No validated cutoff established	decreased	Destruction of IRBC membrane and altered lipid metabolism	Severe malaria and systemic inflammation (Sobota, 2025)
	Free fatty acids	0.1-0.6 mmol/L fasting	No validated cutoff established	Increased	Increased lipid oxidation due to stress response	Metabolic stress and inflammation (Mbuli, 2025)
Purine metabolism	hypoxanthine		No validated cutoff established	Increased	ATP degradation during hypoxia	Marker of tissue hypoxia and severe disease (Mbuli, 2025)
Protein metabolism	urea	2.5-7.1 mmol/L	>20 mmol/L	Increased	Increased protein catabolism and renal impairment	Marker of severe systemic stress and kidney dysfunction (Li, 2025)
Nitric oxide pathway	Nitric-oxide bioavailability		No validated cutoff established	Decreased	Reduced arginine bioavailability and endothelial dysfunction	Contributes to microvascular and tissue hypoxia
Inflammatory cytokine	TNF-α	Assay dependent	No validated universal cutoff	Increased	Parasite triggered immune response	Promotes inflammation, endothelial damage, and severe malaria (Naiing, 2024)
	IL-6	Assay dependent	No validated universal cutoff	Increased	Systemic inflammatory response	Correspond to disease severity and parasite burden (Naiing, 2024)
	IFN-γ	Assay dependent	No validated universal cutoff	Increased	Activation of macrophages and immune response	Associated with immune-mediated tissue damage (Hamad, 2025) (Sadler, 2025)
	IL-10	Assay dependent	No validated universal cutoff	Increased	Anti-inflammatory response to immune activation	Reflects immune regulation during infection. (Naiing, 2024)
Prognostic biomarker	Lactate + TNF-α (combined)			Increased	Interaction between hypoxia and inflammation	Strong predictor of severe malaria outcome (Sobota, 2025)

The combined alterations in glucose metabolism, amino acid metabolism, lipid metabolism and inflammatory cytokines such as IL-10, IFN-γ, IL-6, TNF-α that reflect plasmodium induce metabolic stress, parasite density, host immune response and disease severity.

Integration of multi-omics and artificial intelligence in malaria clinical biochemistry

Despite major development in understanding the biochemical alterations associated with severe malaria, currents tools for diagnosis and prognosis rely solely on conventional laboratory markers like bilirubin, creatinine, lactate and liver enzymes. Although these biomarkers have clinical significance but they lack sufficient specificity and sensitivity for early clinical prediction of disease severity. Hence, future research efforts are now shifting toward integrating clinical biochemistry with high-throughput

molecular approaches and computational prediction models.

Advances in genomics especially whole genome sequencing and genome-wide association studies (GWAS) demonstrate that host genomics variability have a significant effect on severity of malaria, inflammatory response and metabolic disturbances. Similarly, the parasite genomics diversity influences the efficiency of erythrocyte invasion, virulence and metabolic activity of the parasite, all of which translate into measurable biochemical markers.

Recent studies conducted in 2024 demonstrate growing significance of integrating molecular and genomics data into malaria research and control programs in Africa, emphasizing how genomics surveillance can improve disease prediction and biomarker discovery (Tindana, 2024). furthermore, recent identification of plasma protein biomarkers associated with P. falciparum infection, demonstrate the potential of proteomic profiling as a tool for early detection and improved prognosis accuracy of severe malaria (Kanoi, 2025). therefore, integrating genomics, proteomic and metabolomics data is critical for identifying novel markers and understanding the molecular mechanism behind severe malaria (Li, 2025).

Artificial intelligence is emerging as powerful tools for analyzing complex biochemical data in addition to multi-omics approach demonstrating how machine learning and artificial intelligence model can integrate biological, clinical, and environmental data to predict individual malaria risk, and improve early diagnosis (Ribeiro, 2025). similarly, recent studies have shown that AI-based diagnostic models can improve detection accuracy and enable rapid interpretation of molecular and biochemical markers particularly in malaria endemic regions (Alawfi, 2025). in summary, the integration of metabolomics, genomics, proteomic and artificial intelligence based prediction represent the promising avenue for future research, with possibility to transform conventional clinical biochemistry into predictive and personalized approach for early diagnosis, severity stratification, and improved patient care.

Although there is substantial work done on use of AI in diagnosis of malaria, especially the automated parasite detection and classification model using blood smear images. Systemic review conducted in 2024 was able to identify 135 eligible studies of AI/computer-aided malaria parasite detection and classification (Flavia Grignaffin, 2024). More recent systemic review and met-analysis of clinically validated AI malaria diagnostic studies reported pool sensitivity of approximately 87% and specificity of 88.3% and sensitivity of 90.7% against PCR (icha Farihah Deniyati Faratisha, 2026).

AI in malaria is not merely hypothetical. However, most established applications have been on diagnosis by image-based parasite detection rather than integrated prediction of disease severity through biochemical and multi-omics data analysis.

Table 6: Oxidative stress parameter and their alteration in malaria infection

category	Biochemical marker	Reference range	Severe malaria threshold	Alteration	Underlying mechanism	Clinical significance
Glucose metabolism	Blood glucose	3.9 – 5.5 mmol/L	<2.2mmol/L	Decrease	Increase glucose consumption by the parasite and reduce hepatic gluconeogenesis	Hypoglycemia associated with coma, seizures and severe malaria (Li, 2024)
Lactate metabolism	Blood lactate	0.5 – 2.2 mmol/L	≥5 mmol/L	Increased	Tissue hypoxia, anaerobic glycolysis and parasite metabolism	Indicate metabolic acidosis (strong prognostic marker) (Ishola, 2024)
Energy metabolism	pyruvate	0.03-0.10 mmol/L	No validated cutoff established	increased	Accelerated glycolysis due to hypoxia	Indicates impaired oxidative metabolism (Mbuli, 2025)
	ATP production		No validated cutoff established	Decreased	Mitochondrial dysfunction and tissue hypoxia	Lead to organ failure in severe malaria (Mbuli, 2025)
Amino acid metabolism	Arginine	50-150 µmol/L	No validated cutoff established	Decreased	Reduced nitric oxide synthesis and endothelial dysfunction	Promote microvascular damage and severe malaria (Sobota, 2025)
	Phenylalanine	35-85 µmol/L	No validated cutoff established	Increased	Impaired liver function and alteration of amino acid metabolism	Associated with severity of malaria (Mbuli, 2025)
	Tryptophan	40-90 µmol/L	No validated cutoff established	Decreased	Immune-mediated metabolism through indoleamine pathway	Reflects immune activation and inflammation (Sobota, 2025)
Lipid metabolism	Lysophosphatidylcholines (LPCs)		No validated cutoff established	decreased	Destruction of RBC membrane and altered lipid metabolism	Severe malaria and systemic inflammation (Sobota, 2025)
	Free fatty acids	0.1-0.6 mmol/L fasting	No validated cutoff established	Increased	Increased lipid oxidation due to stress response	Metabolic stress and inflammation (Mbuli, 2025)
Purine metabolism	hypoxanthine		No validated cutoff established	Increased	ATP degradation during hypoxia	Marker of tissue hypoxia and severe disease (Mbuli, 2025)
Protein metabolism	urea	2.5-7.1 mmol/L	>20 mmol/L	Increased	Increased protein catabolism and renal impairment	Marker of severe systemic stress and kidney dysfunction (Li, 2025)
Nitric oxide pathway	Nitric-oxide bioavailability		No validated cutoff established	Decreased	Reduced arginine bioavailability and endothelial dysfunction	Contributes to microvascular and tissue hypoxia
Inflammatory cytokine	TNF-α	Assay dependent	No validated universal cutoff	Increased	Parasite triggered immune response	Promotes inflammation, endothelial damage, and severe malaria (Niang, 2024)
	IL-6	Assay dependent	No validated universal cutoff	Increased	Systemic inflammatory response	Correspond to disease severity and parasite burden (Niang, 2024)
	IFN-γ	Assay dependent	No validated universal cutoff	Increased	Activation of macrophages and immune response	Associated with immune-mediated tissue damage (Hamd, 2024) (Sadler, 2025)
	IL-10	Assay dependent	No validated universal cutoff	Increased	Anti-inflammatory response to immune activation	Reflects immune regulation during infection (Niang, 2024)
Prognostic biomarker	Lactate + TNF-α (combined)			Increased	Interaction between hypoxia and inflammation	Strong predictor of severe malaria outcome (Sobota, 2025)

Current evidences distinguish an established or clinically evaluated AI models from emerging research directions. The proposed multi-omics application is not meant to be interpreted as clinically validated technologies. Their translation into clinical practice requires prospective multicenter studies, independent external validation, assessment of discrimination and calibration, analysis of clinical utility, subgroup performance evaluation and potential algorithmic bias.

The critical translational opportunity extracted from the available literature driven evidence is the integration of routine biochemical markers with metabolomics, proteomics, transcriptomics/genomics and clinical data to develop and externally validate multimodal predictive models for severe malaria outcomes.

Such approach could move beyond single-biomarker assessment by using complementary information across metabolic, inflammatory, molecular and clinical domain, while improving risk stratification for outcome like severe malaria, AKI, cerebral involvement, metabolic acidosis, multi-organ dysfunction, and mortality.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

All authors have read and consented to the submission of the manuscript.

Availability of data and material

Not Applicable.

Competing interests

All authors declare no competing interests.

Funding

Acknowledgment

References

(CDC), C. f. (2024). *Clinical features of malaria*. Atlanta (GA): CDC. Retrieved from <https://www.cdc.gov/malaria/hcp/clinic202a1-features/index.html>.

(CDC, C. f. (2024). *Clinical guidance: malaria diagnosis and treatment in the U.S*. Atlanta (GA): CDC. Retrieved from <https://www.cdc.gov/malaria/hcp/clinic202a1-features/index.html>.

Lendongo Wombo, J. B.-L.-N.-D. (2023). Severe malaria in children and adolescents in Southeast Gabon. *BMC infectious diseases*, 23(1), 207. doi:<https://doi.org/10.1186/s12879-023-08133-y>.

Alam, N. F. (2026). Erythrocyte invasion in malaria: from molecular mechanisms to rational vaccines. *Nature reviews. Microbiology*, 24(2), 97–110. doi:<https://doi.org/10.1038/s41579-025-01235-1>.

Alawfi, B. (2025). Hybrid Capsule Network for precise and interpretable detection of malaria parasites in blood smear images. *Frontiers in cellular and infection microbiology*, 15, 1615993. doi:<https://doi.org/10.3389/fcimb.2025.1615993>

Alves-Rosa, M. F. (2024). P. falciparum Invasion and Erythrocyte Aging. *cells*, 13(4), 334. doi: <https://doi.org/10.3390/cells13040334>.

Aramburo A, T. J. (2018). Lactate clearance as a prognostic marker for mortality in severe febrile children in East Africa. *BMC Medicine*, 16(1), 37. Retrieved from <https://doi.org/10.1186/s12916-018-1014-x>.

Bachmann, A. e. (2022). CD36-A Host Receptor Necessary for Malaria Parasites to Establish and Maintain Infection. *Microorganisms*, 10(12), 2356. doi:<https://doi.org/10.3390/microorganisms10122356>.

- Basire, B. e. (2025). Evaluation of serum electrolytes and kidney function among untreated malaria (*Plasmodium falciparum*) patients in health centers, Konso zone, South Ethiopia. *Tropical diseases, travel medicine and vaccines*, 11(11), 29. doi:doi:10.1186/s40794-025-00265-0.
- Bernabeu, M. a. (2017). EPCR and Malaria Severity: The Center of a Perfect Storm. *Trends in parasitology*, 33(4), 295-308. doi:doi:10.1016/j.pt.2016.11.004.
- Bissinger, R. Q. (2024). Eryptosis: a driver of anemia in chronic kidney disease. *Current opinion in nephrology and hypertension*, 33(2), 220–225. doi:https://doi.org/10.1097/MNH.0000000000000957.
- Carret, V. e. (2025). Post-artesunate Delayed Hemolysis in African Children With Severe Malaria: Incidence, Medical Impact and Prevention. *Clinical infectious diseases. an official publication of the Infectious Diseases Society of America*, 81(2), 389-396. doi:doi:10.1093/cid/ciaf067.
- Centers for Disease Control and Prevention. (2024). *Malaria biology: Life cycle*. Atlanta (GA): CDC. Retrieved from <https://www.cdc.gov/dpdx/malaria/>.
- Chughlay, M. F. (2020). Liver Enzyme Elevations in *Plasmodium falciparum* Volunteer Infection Studies: Findings and Recommendations. *The American journal of tropical medicine and hygiene*, 103(1), 378-393. doi:doi:10.4269/ajtmh.19-0846.
- Cobbold, S. A. (2016). Metabolic Dysregulation Induced in *Plasmodium falciparum* by Dihydroartemisinin and Other Front-Line Antimalarial Drugs. *The Journal of infectious diseases*, 213(2), 276-86. doi:doi:10.1093/infdis/jiv372.
- Cowman, A. F. (2017). The Molecular Basis of Erythrocyte Invasion by Malaria Parasites. *Cell host & microbe*, 22(2), 232-245. doi:doi:10.1016/j.chom.2017.07.003.
- Cowman, A. F. (2017). The Molecular Basis of Erythrocyte Invasion by Malaria Parasites. *Cell host & microbe*, 22(2), 232–245. doi:https://doi.org/10.1016/j.chom.2017.07.003.
- Deroost, K. e. (2016). Immunological balance between host and malaria. *FEMS microbiology reviews*, 40(2), 208-57. doi:doi:10.1093/femsre/fuv46.
- Derwesh SA, F. A. (2025). Impact of Malaria Severity on Selected Liver Function Markers in Aden, Yemen: A Pilot Study. *Yemeni Journal for Medical Sciences*, 19(4). doi:https://doi.org/10.20428/yjms.v19i4.2852.
- Flavia Grignaffin, P. S. (2024). computer-aided diagnosis system for automatic malaria parasite detection and classification: a systemic review. *MDPI*, 13(16), 3174. Retrieved from <https://doi.org/10.3390/electronics13163174>.
- Frischknecht, F. a. (2017). *Plasmodium Sporozoite Biology. Cold Spring Harbor perspectives in medicine*, 7(5), a025478. doi:doi:10.1101/cshperspect.a025478.
- Ganz, T. &. (2012). Hepcidin and iron homeostasis. *Biochimica et biophysica acta*, 1823(9), 1434–1443. doi:https://doi.org/10.1016/j.bbamcr.2012.01.014.
- Gill, J. e. (2023). sion molecule-1 (ICAM-1) shed light on population-specific malaria susceptibility. *MC genomicS*, 24(1), 773. doi:doi:10.1186/s12864-023-09846-9.
- Glatt, T. a. (2025). The role of red cell exchange in the management of malaria in 2024; Transfusion and apheresis science. *official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*, 64(3), 104146. doi:doi:10.1016/j.transci.2025.104146.
- Gomes, A. R. (2022). Oxidative Stress in Malaria: Potential Benefits of Antioxidant Therapy. *International journal of molecular sciences*, 23(11), 5949. doi:https://doi.org/10.3390/ijms23115949.
- Gupta, A. e. (2025). Emerging Role of Splenic Macrophage in Malaria Pathogenesis and Immunity. *Immunity, inflammation and diseases*, 13(10), e70258. doi:doi:10.1002/iid3.70258.
- Gupta, P. P. (2022). Heme Detoxification Protein (PfHDP) is essential for the hemoglobin uptake and metabolism in *Plasmodium falciparum*. *ASEB bioAdvances*, 4(10), 662–674. doi:https://doi.org/10.1096/fba.2022-00021.
- icha Farihah Deniyati Faratisha, K. C. (2026). diagnostic accuracy of using artificial intelligence for malaria diagnostic: AI System review and meta-analysis. *infectious disease reports*, 18(1), 11. Retrieved from <https://doi.org/10.3390/idr18010011>.
- Jensen, A. R. (2020). “Cerebral *Plasmodium falciparum* malaria: The role of PfEMP1 in its pathogenesis and immunity, and PfEMP1-based vaccines to prevent it. *mmunological*

- reviews, 293(1), 230-252.
doi:doi:10.1111/imr.12807.
- Kanoi, B. N. (2025). Plasma protein biomarkers of Plasmodium falciparum infection in pregnant women: a high-throughput proteomics study. *Frontiers in cellular and infection microbiology*, 15, 1594088. doi:doi:10.3389/fcimb.2025.1594088.
- Kazing, C. e. (2025). Acute Kidney Injury in Severe Malaria: A Serious Complication Driven by Hemolysis. *Seminars in nephrology*, 45(3), 151614. doi:doi:10.1016/j.semnephrol.2025.151614
- Li, Q. L. (2025). Malaria: past, present, and future. *Sig Transduct Target Ther*, 10, 188. doi:https://doi.org/10.1038/s41392-025-02246-3.
- Liu, F. F. (2025). Malaria and dyserythropoiesis: a mini review. *Frontiers in cellular and infection microbiology*, 15, 1679337. doi:https://doi.org/10.3389/fcimb.2025.1679337.
- Lu, J. e. (2025). The contrasting effects of two antimalarial drugs on insulin secretion. *Cellular and molecular life sciences*, 82(1), 419. doi:doi:10.1007/s00018-025-05933-0.
- Meena, P. S. (2026). Clinical characteristics and outcome of malaria-associated acute kidney injury in adult patients; a systematic review and meta analysis. *Malaria Journal*, 25, 122. doi:https://doi.org/10.1186/s12936-025-05777-w.
- Merga, H. D. (2025). Urban malaria and population mobility in sub-Saharan Africa: systematic review and meta-analysis. *Malaria journal*, 24(1), 264. doi:https://doi.org/10.1186/s12936-025-05508-1.
- Moxon, C. A. (2020). New Insights into Malaria Pathogenesis. *Annual review of pathology*, 15, 315–343. doi:https://doi.org/10.1146/annurev-pathmechdis-012419-032640.
- Ohiaigu, F. O.-O. (2021). Pathophysiology of severe malaria infection. *Asian Journal of Health Sciences*, 7(2), ID22-ID22. doi:DOI:10.15419/ajhs.v7i2.492.
- Okagu, I. U. (2022). Molecular mechanisms of hematological and biochemical alterations in malaria: A review. *Molecular and biochemical parasitology*, 247(1), 111446. doi:https://doi.org/10.1016/j.molbiopara.2021.111446.
- Okello, G. A. (2026). Malaria: a review on its current epidemiological status and management strategies. *Malaria Journal*, 25, 132. doi:https://doi.org/10.1186/s12936-025-05748-1.
- Oluwatuyi KO, A. A. (2024). . Serum Cystatin C as an Index of Early Detection of Acute Kidney Injury in Children With Severe Malaria. *World Journal of Nephrology and Urology*, 13(1), 19-25. doi:https://doi.org/10.14740/wjnu445.
- Othman, B. e. (2023). Different PfEMP1-expressing Plasmodium falciparum variants induce divergent endothelial transcriptional responses during co-culture. *PloS one*, 18(11), e0295053. doi:doi:10.1371/journal.pone.0295053.
- Pikor, D. e. (2025). Neurovascular Pathophysiology and Emerging Biomarkers in Cerebral Malaria: An Integrative Perspective. *Neurology international*, 17(9), 149. doi:doi:10.3390/neurolint17090149.
- Possemiers, H. V. (2021). Etiology of lactic acidosis in malaria. *PLoS pathogens*, 17(1), e1009122. doi:https://doi.org/10.1371/journal.ppat.1009122.
- Prenen, F. a. (2025). Malaria-associated liver dysfunction: a forgotten challenge. *Trends in parasitology*, 41(7), 547-559. doi:doi:10.1016/j.pt.2025.05.010.
- Prenen, F. V. (2025). JAK/STAT inhibition protects glucocorticoid receptor knockout mice from lethal malaria-induced hypoglycemia and hyperinflammation. *EMBO molecular medicine*, 17(8), 2040–2070. doi:https://doi.org/10.1038/s44321-025-00264-w.
- Ribeiro, A. H. (2025). From bites to bytes: understanding how and why individual malaria risk varies using artificial intelligence and causal inference. *Frontiers in genetics*, 16, 1599826. doi:doi:10.3389/fgene.2025.1599826.
- Risco-Castillo, V. S. (2013). Phase hépatique du paludisme : voies d'entrée des sporozoïtes de Plasmodium [Plasmodium sporozoite entry pathways during malaria liver infection]. *Biologie aujourd'hui*, 207(4), 219–229. doi:https://doi.org/10.1051/jbio/2013021.
- Sakoguchi, A. a. (2022). Mechanisms for Host Immune Evasion Mediated by Plasmodium falciparum-Infected Erythrocyte Surface Antigens. *Frontiers in immunology*, 13, 901864. doi:doi:10.3389/fimmu.2022.901864.
- Segbefia, S. P. (2024). Cytokine gene polymorphisms implicated in the pathogenesis of Plasmodium falciparum infection outcome.

- Frontiers in immunology*, 15, 1285411. doi:doi:10.3389/fimmu.2024.1285411.
- Siddig AM, M. M. (2026). Effect of Severe Malaria on Biochemical Markers (Liver Functions Tests) among Severe Malaria Patients Attending to Kosti Teaching Hospital, White Nile state. *Asian Journal of Medical Principles and Clinical Practice*, 9(1), 100-6. doi:doi:10.9734/ajmpcp/2026/v9i1381.
- Sobota, R. S. (2025). A shared inflammatory signature across severe malaria syndromes manifested by transcriptomic, proteomic and metabolomic analyses. *Nature communications*, 16(1), 4620. doi:doi:10.1038/s41467-025-59281-5.
- Tan, M. S. (2021). Malaria parasite egress at a glance. *ournal of cell science*, 134(5), jcs257345. doi:https://doi.org/10.1242/jcs.257345.
- Tandoh KZ, D.-Q. N.-O. (2024). Editorial: Malaria molecular epidemiology current situation in Africa. *Editorial: Malaria molecular epidemiology current situation in Africa.*, 4, 400612. doi:doi:10.3389/fepid.2024.1400612.
- Tindana, P. e. (2024). Researchers' perspectives on the integration of molecular and genomic data into malaria elimination programmes in Africa: a qualitative study. *Malaria journal*, 23(1), 385. doi:doi:10.1186/s12936-024-05205-5.
- van Niekerk, D. D. (2023). A detailed kinetic model of glycolysis in Plasmodium falciparum-infected red blood cells for antimalarial drug target identification. *The Journal of biological chemistry*, 299(9), 105111. doi:https://doi.org/10.1016/j.jbc.2023.105111.
- van Schuijlenburg, R. A. (2024). Ageing of Plasmodium falciparum malaria sporozoites alters their motility, infectivity and reduces immune activation in vitro. *Malaria Journal*, 23, 111. doi: https://doi.org/10.1186/s12936-024-04946-7.
- Vaughan, A. M. (2017). Malaria Parasite Liver Infection and Exoerythrocytic Biology. *Cold. Spring Harbor perspectives in medicine*, 7(6), a025486. doi:https://doi.org/10.1101/cshperspect.a025486.
- White, N. (2018). Anemia and Malaria. *Malaria Journal*, 17, 371. doi:doi.org/10.1186/s12936-018-8.
- White, N. (2022). Severe Malaria. *Malaria Journal*, 2022, 284..
- Wiser, M. F. (2023). Knobs, Adhesion, and Severe Falciparum Malaria. *tropical medicine and infectious disease*, 8(7), 353. doi:doi:10.3390/tropicalmed8070353.
- Wiser, M. F. (2024). The Digestive Vacuole of the Malaria Parasite: A Specialized Lysosome. *athogens (Basel, Switzerland)*, 13(2), 182. doi:doi:10.3390/pathogens13030182
- World Health Organization. (2024). *WHO Malaria Policy Advisory Group (MPAG) meeting report, 4, 5 and 7*. Geneva: WHO. Retrieved from. <https://iris.who.int/server/api/core/bitstreams/ebeea27d-2ce7-43a0-be60ffb830dbe382/content>.
- World Health Organization. (2024). *World malaria report*. Geneva: WHO. Retrieved from <https://cdn.who.int/media/docs/default-source/malaria/world-malaria-reports/world-malaria-report-2024-spreadview.pdf?>.
- World Health Organization. (2024). *World malaria report*. Geneva: WHO. Retrieved from <https://cdn.who.int/media/docs/default-source/malaria/world-malaria-reports/world-malaria-report-2024-spreadview.pdf?>.
- World Health Organization. Malaria. (2025). *Malaria*. geneva: WHO. Retrieved from www.who.int/news-room/fact-sheets/detail/malaria.
- Yakubu, M. N. (2024). Host metabolomic responses in recurrent P. vivax malaria. *Scientific reports*, 14(1), 7249. doi:doi:10.1038/s41598-024-54231-5.