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Review Article

Pathological basis of severe malaria in children: investigating immune dysregulation, organ-specific damage, and long-term outcomes

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ABSTRACT

Malaria is a globally endemic parasitic disease, particularly prevalent in tropical regions and primarily affecting children and pregnant women. Comprehending the pathological mechanisms underlying severe malaria is crucial for enhancing treatment outcomes and decreasing mortality rates. This study aims to investigate immune dysregulation in severe malaria, explore organ-specific damage resulting from malaria infections in children, and examine long-term health consequences in survivors of severe malaria. This literature review involved an extensive literature search across electronic databases including PubMed, Google Scholar, Scopus, and Web of Science using keywords such as: severe malaria, children, immune dysregulation, organ-specific damage, and outcomes from 2015 to 2025. The study found cytokine imbalance and endothelial dysfunction due to immune dysregulation, liver and kidney dysfunction, and hematological changes due to severe malaria. To prevent the consequences of severe malaria in children, awareness and early detection of malaria signs and symptoms, next-generation sequencing, proteomics, and metabolomics, as well as regional and community-based malaria research, are required.

Keywords: Severe malaria, Children, Immune dysregulation, Organ-specific damage, Outcomes

INTRODUCTION

Malaria is a globally prevalent parasitic disease.[1] It is especially widespread in tropical regions and primarily affects children and pregnant women.[1] It disproportionately affects children under five years old.[2] It is endemic in areas such as sub-Saharan Africa and parts of Asia, and Oceania.[2] Malaria is a major cause of illness and death among young children in these areas.[2] The most lethal species responsible for severe cases and

high mortality rates is *Plasmodium falciparum*.[2] In Africa alone, falciparum malaria causes over 200,000 child deaths every year.[2] Understanding the pathological mechanisms of severe malaria is important for improving treatment outcomes and reducing mortality rates. Severe malaria involves complex pathophysiological processes. These can cause life-threatening complications before antimalarial drugs start working.[3] Research into these mechanisms is essential. This helps create more therapies to go along with current treatments.[3] These can improve survival rates.[3] Clinical studies are currently going on to find new treatment targets and better manage severe malaria in children.[3]

The need for improved diagnostics, treatment, and prevention strategies is important to combat this disease effectively. Recent advancements, such as the development of vaccines like RTS, S/AS01, and new chemoprevention guidelines, offer new hope for reducing malaria cases and deaths.[4] Certain challenges such as antimalarial drug resistance, remain.[2] Continued research and innovation in diagnostics, treatment, and prevention are essential to achieving global malaria control and elimination goals.[4] This study aims to investigate immune dysregulation in severe malaria, explore organ-specific damage resulting from malaria infections in children, and determine long-term health consequences in survivors of severe malaria.

METHODS

This is a literature review that involved an extensive literature search across electronic databases including PubMed, Google Scholar, Scopus, and Web of Science using keywords such as: severe malaria, children, immune dysregulation, organ-specific damage, and outcomes from 2015 to 2025. Inclusion criteria were studies such as cross-sectional studies, longitudinal studies, case-series, case-reports, systematic reviews, meta-analyses, and literature reviews that focused on the study's aim and objectives, written in English. Exclusion criteria were studies such as editorials, letters to the editors, opinions, commentaries, and perspectives.

DISCUSSION

Pathophysiology of severe malaria

Severe malaria, mainly caused by *Plasmodium falciparum*, is a life-threatening condition that is especially harmful to children. To develop effective treatments and prevention strategies, it is important to understand how this severe form of malaria develops.

Overview of malaria pathogenesis

Malaria is caused by unicellular protozoan parasites that belong to the genus *Plasmodium*.[5] These parasites affect humans and other vertebrates like reptiles, birds, and mammals.[5] The five *Plasmodium* species that infect humans and cause malaria are *P. falciparum, P. vivax, P. malariae, P. ovale, and P. knowlesi*.[5] The first four species only infect humans, while *P. knowlesi* can also be found in macaque monkeys[5]. The complex life cycle involves both mosquito and human hosts. In humans, these parasites multiply inside red blood cells, causing fever and anemia.[5,6] In severe cases, they can lead to serious complications such as loss of consciousness, coma, and even death.[6]

The malaria parasite protects its proteins under stress, especially in red blood cells (RBCs).[7] Heat shock proteins help maintain protein stability (proteostasis).[7] Once inside RBCs, the parasite releases proteins, including chaperones, to change the cell.[7] This helps it survive and cause disease. Both the parasite and the host cell have chaperones that assist with protein folding and function.[7] The transmission of *Plasmodium* species depends on an insect vector, which is usually a mosquito.[5] The *Plasmodium's* sexual reproduction occurs inside the mosquito.[5] This development in the mosquito is important for the parasite to be transmitted to the next vertebrate host.[5] *Plasmodium* species have great genetic flexibility.[5] This flexibility helps them adapt to environmental changes.[5] It allows them to quickly develop resistance to treatments like antimalarials.[5] It also enables them to change their host preferences.[5]

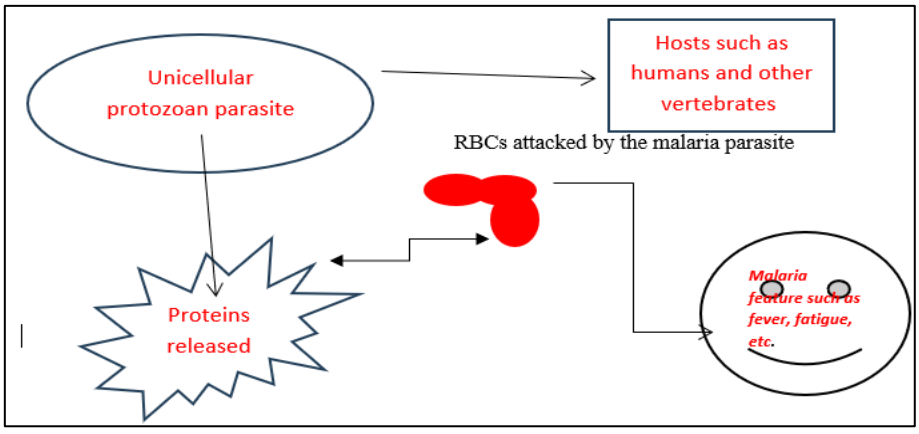

Figure 1: Summary of malaria pathogenesis.

Role of plasmodium species in causing severe malaria in children

P. falciparum is the most virulent species of all the malaria species, responsible for the majority of severe malaria cases and deaths, especially in children.[8] In severe malaria, the disease process involves the sequestration of infected red blood cells in small blood vessels.[9] This is caused by surface proteins like PfEMP1, which help the infected cells stick to the vessel walls and avoid the immune system.[9] Severe falciparum malaria includes many diseases.[8] Its development can be influenced by age, exposure, and immune status.[8] It can cause complications in specific organs, like the brain in cerebral malaria (CM) or the placenta in malaria during pregnancy (MiP).[8] The spleen filters infected and altered red blood cells.[10] This filtering can affect the severity of the disease.[10] In children, the impact might be different because their immune responses vary compared to adults.[10] A study suggests a hypothesis that coevolution increases the splenic clearance of *P. falciparum*-altered red blood cells in children.[10] This favors host survival and supports continued parasite transmission.[10]

Immune response in severe malaria

Severe malaria triggers a complex immune response that involves both innate and adaptive immune systems. Sometimes, these reactions can become unbalanced, leadi ng to serious health issues. Understanding how this happe ns is essential for creating better treatments and the prevention methods.

Innate and adaptive immune responses to malaria

When the body first responds to an infection, it plays an important role in determining how severe malaria will be.[11] The complement system is essential in starting and enhancing this immune response.[11] It triggers inflammation, endothelial activation, opsonization, and coagulation.[11] However, excessive activation can lead to severe disease.[11] This balance is crucial in managing the severity and outcome of malaria. Innate immune responses regulate adaptive immunity.[12] Adaptive responses involve T and B cells, which are important for long-term immunity.[13] However, children often do not develop a complete and effective long-term immune response against malaria.[13] Severe malaria is linked to an imbalance in cytokine production.[14] This includes both pro-inflammatory cytokines like TNF and IL-6, and regulatory cytokines like IL-10.[14] When this balance is disrupted, it can result in excessive inflammation and damage to tissues.[14] Altered T and B cell responses can impair the development of effective immunity, which contributes to disease severity.[13] The symptoms of severe falciparum malaria can change based on how common the infection is in an area.[15] Severe cases usually involve one or more serious complications, such as cerebral malaria, hyperparasitemia, hypoglycemia, severe malarial anemia (SMA), and respiratory difficulties.[15] In areas where malaria is always present, >30% of children with severe SMA may not survive.[15] In SMA, many processes contribute to destruction of RBCs.[15] This includes both infected and non-infected RBCs.[15] Production of new RBCs (erythropoiesis) is either inefficient or suppressed, and there is also abnormal development of RBCs (dyserythropoiesis).[15] All of these factors can lead to lower hemoglobin levels in individuals with malaria.[15]

There are some differences between immune responses in children and adults. Young children are at a higher risk of severe illness and death from malaria. Their immune response is different from that of adults, which makes them more vulnerable to severe malaria and slows down the development of their immunity. A study suggests that both regulatory and pro-inflammatory responses become less intense as children grow older. Repeated exposure to malaria allows adults to develop a more controlled immune response. This regulation helps in managing inflammation and reducing the severity of the disease.[14]

Immune dysregulation in severe malaria

Severe malaria includes complex immune responses that can lead to morbidity and mortality. Understanding immune dysregulation, like cytokine imbalance and endothelial dysfunction, is important for developing effective treatments and interventions. Malaria is a complicated disease that is not fully understood. When the malaria parasite enters the bloodstream, the body's immune system starts producing substances called cytokines, like IL-6, IL-8, IFN-γ, and TNF.[16] These cytokines help to control and eliminate the parasite.[16] There are also other cytokines called the regulatory cytokines, such as TGF-β and IL-10.[16] They keep a balance between the body's inflammatory and anti-inflammatory responses.[16] However, cytokines have a double role as they help to clear the parasite and can also cause the harmful symptoms seen in malaria.[16] When there's an imbalance in these mediators, it can cause the immune system to overreact.[17] This overactivation can worsen the disease and lead to severe symptoms like cerebral malaria and severe anemia.[18]

The invasion of endothelial cells by malaria parasites can lead to many changes, contributing to blood vessel problems and complications such as cerebral malaria.[16,17] In cerebral malaria, neurological symptoms are caused by disruption of the blood-brain barrier (BBB) due to inflammation and endothelial cell damage.[16,17] Infected red blood cells get stuck in small blood vessels, which blocks blood flow and oxygen delivery to essential organs. This worsens organ function and leads to severe disease outcomes.[16,17] Children show different immune responses compared to adults.[14] There are age-related variations in cytokine production, which affect how severe disease can be.[19] Genetic factors can impact how immune system responds to severe malaria. Differences in cytokine gene expression and immune regulation can affect disease severity.[20]

Table 1: Cytokine imbalance in severe malaria.

Cytokine type	Examples	Function	Role in severe malaria	References
Pro-inflammatory cytokines	IL-6, IL-8, IFN-γ, TNF	Aid in parasite clearance by activating immune responses	Excessive production leads to immune overactivation, contributing to severe symptoms such as cerebral malaria and anemia	16-18
Regulatory cytokines	TGF-β, IL-10	Maintain a balance between inflammatory and anti-inflammatory responses	Imbalance can cause either excessive inflammation or immune suppression, increasing disease severity	16, 17
Endothelial dysfunction	-	Involves inflammatory damage to blood vessels and endothelial cells	Leads to BBB disruption, contributing to cerebral malaria and vascular complications	16, 17
Age-related cytokine variations	-	Cytokine production differs between children and adults	Alters disease severity based on age-related immune responses	19
Genetic factors in immune regulation	-	Variations in cytokine gene expression influence immune response	Affects the susceptibility and severity of severe malaria	20

Organ-specific damage in severe malaria

Neurological complications (cerebral malaria)

The brain contains a network of blood vessels that are necessary for providing nutrients and oxygen, and for removing carbon dioxide and wastes. This network of capillaries, together with the glia, forms a protective barrier called the BBB. This barrier prevents large molecules and pathogens in the blood from entering the brain tissues and therefore altering the brain's functions.[21,22] Patients infected with the malaria parasite *P. falciparum* may develop a diffuse, reversible encephalopathy, termed cerebral malaria. When the brain barrier was studied, it was found that functional changes to the BBB occur in cerebral malaria, possibly as a result of the binding of parasitized RBC to cerebral endothelial cells.[23] Platelet adhesion to brain endothelial cells can also lead to modifications of the BBB, showing that it potentiates endothelial cell apoptosis.[24] To detect this breakdown, different screening and imaging tools were used, like radiological approaches, examining cerebral blood flow, as well as ophthalmoscopic examination of the retina, since it also gives a valuable insight into BBB function and its properties during the disease.[25] Managing the case suffering from neurological involvement involves putting the patient into the left lateral position, checking the blood glucose, and administering oxygen if hypoxic. Benzodiazepines, particularly diazepam, are used as the initial anticonvulsants. Phenobarbital and phenytoin are used as second-line treatments, as prompt and effective management of falciparum malaria-associated convulsions may contribute to a better outcome in children with severe malaria.[26] To treat the neuroinflammation induced by malaria, artemisinins were found to be effective, both in direct (via regulating inflammatory process in the CNS, exerting anti-oxidative stress and neuroprotective effect, and preventing Aβ accumulation) and indirect (via maintaining BBB integrity, suppressing systemic inflammation and alleviating intestinal inflammation) manner.[27]

Liver and kidney dysfunction

Kidney complications in malaria mainly occur either due to hemodynamic dysfunction or due to immune response. Histologic studies support glomerulonephritis, acute tubular necrosis (ATN), and acute interstitial nephritis (AIN).[28,29] It is also possible to find chronic kidney disease (CKD) associated with malaria, mainly in patients suffering from repeated episodes of malaria, and *Plasmodium* antigens can readily be detected in the glomeruli of these patients. Similarly, liver complications in malaria are also common, and hepatomegaly, jaundice, and hepatic dysfunction further worsen the acute kidney injury (AKI), though not completely understood, by far the most accepted mechanisms of acute kidney injury in malaria include impediments in renal microcirculation, infection-triggered proinflammatory reactions within the kidney, and metabolic disturbances.[28,29]

Pulmonary and cardiovascular implications

Dyspnea in patients with malaria should alert clinicians to the respiratory distress syndrome (RDS), with a poor prognostic factor. This syndrome manifests with cough, dyspnea and refractory hypoxemia. Patients should be admitted to intensive care units and treated with parenteral antimalarial drug treatment and ventilatory

and hemodynamic support without delay.[30] The severity of pulmonary impairment in patients with malaria is determined not only by initiation of antimalarial treatment but also by host's associated immune response.[31] Since the main problems of this syndrome are presence of inflammatory infiltrate, hemorrhages, and edema, it greatly interferes with gas exchange capacity of lungs.[32] CVS complications also studied, indicating involvement of system in severe malaria cases as evidenced from ECG and echocardiography, and that cardiovascular instabilities are common not only in *falciparum malaria*, but can also be observed in *vivax malaria*.[33]

Hematological changes

Malaria worsens the condition of a patient suffering from anemia as it causes hemolysis of infected and uninfected erythrocytes and bone marrow dyserythropoiesis, which compromises rapid recovery from anemia, and in severe cases, the mortality of severe malaria rises steeply below an admission hemoglobin of 3 g/dL.[34] Since the relationship between the severity of anemia and other nutritional deficiencies in the pathogenesis of malaria infection was confirmed, it was, therefore, recommended that the immunomodulation potential of micronutrients may be essential in the management of malaria infection.[35] Other than affecting the red blood cells, platelets were also found to be affected, and alterations of blood coagulation are thought to be involved in malaria pathogenesis, suggesting that a hypercoagulable state may be induced, even when parasite density is low. In one of the case reports, the challenges posed by consecutive recurrent intracranial bleeds following traumatic brain injury (TBI) were exacerbated by *P. falciparum* infection. It highlights the nature of malaria-induced coagulopathy and emphasizes the importance of timely and aggressive interventions in managing such cases.[36]

Table 2: Organ-specific damage in severe malaria.

Involved organ(s)	Parenchymatous changes	Inciting event	References
Neurological complications	BBB integrity is lost	Glial cell damage	21-24
Liver and kidney dysfunction	Renal glomerulus and hepatic cells.	AKI and jaundice.	28 and 29
Pulmonary and cardiovascular implications	Endocardium and alveolar membranes.	Hypoxia, ischemia, and MI.	30-32
Hematological changes	RBCs and platelets are damaged.	Nutritional deficiency.	34-36

Very long-term outcomes and sequelae in survivors

Cognitive and developmental delays

Malaria can have serious consequences on the nervous system. It increases the risk for gross motor, communication, and personal social delay, and further analyses suggested that anaemia was a significant mediator in the pathway between malaria infection and risk for these delays.[37] A study by Boivine, showed that controls scored significantly better on the Kaufman assessment (KABC-II), global domains, as well as on the mental processing index, than their retinopathy-positive cerebral malaria (CM-R) counterparts, and it was found that as a result of developmental delays due to malaria, low performance results were observed on all of the assessment scales, compared to the unexposed group.[38,39] One of the attributed reasons to these findings was ischemic neural injury caused as a result of cerebral malaria, and prompt follow-up, diagnosis, and interventions for these children were considered necessary and if the treatment is delayed, cognitive developmental delay would result in long-term internalizing(anxiety, depression) and externalizing (aggression) behavioral problems in children under <5 years of age.[40,41]

School performance was shown to decline following multiple malaria attacks; when evaluated, the mean scores for both mathematics and Thai language significantly decreased with the increasing number of malaria attacks. Students who had a history of five or more malaria episodes had lower scores in mathematics and Thai language, and hence a lower school performance than those who had only one or two malaria episodes.[42] Similarly, in another study, declining school performance was observed in African schoolchildren, and intermittent preventive treatment of malaria improved outcomes.[43]

Chronic organ dysfunction

The malaria parasite pursues a complicated life cycle in an invertebrate, mosquito, and vertebrate host with several distinct stages, which play an important part in its effects on multiple organs. In the human host, it invades the liver and RBCs to complete its life cycle. Moreover, patients recovered from severe malaria may suffer throughout their life from impairments in organ function such as loss of eyesight, kidney failure, and much more.[44] Renal dysfunction is characterized by an increase in creatinine, urea, and some of the electrolytes in the serum, while hepatic dysfunction is characterized by an increase in liver enzyme activities, and renal and hepatic dysfunctions are part of the pathological effects of malaria infection, common in children and pregnant women.[45] Conroy described in his study that AKI is a recognized complication of pediatric severe malaria.[46] The haematological changes in severe malaria, characterized by anaemia, dyserythropoiesis,

thrombocytopenia, and coagulopathy, significantly contribute to the disease's morbidity and mortality.[47]

Cardiovascular health post malaria

Cardiovascular complications were defined as abnormalities in electrocardiogram (ECG), cardiac biomarkers, and echocardiography on admission or during outpatient examination. The most common cardiovascular pathologies related to malaria patients were myocarditis and acute coronary syndrome (ACS), and evidence of parasitized RBCs in the myocardium. Cardiovascular complications are not uncommon in symptomatic adults and children with malaria and that children exposed to malaria had high blood pressure (BP) in adulthood.[48,49] However, only pulmonary pressure was found to be raised in both pediatric and adult patients suffering from malaria, while the systemic vascular resistance had no significant changes.[50]

Psychosocial and economic impacts

Higher income for individuals or countries improves health through different channels, from better nutrition to better public health infrastructure.[51] A study conducted in Kenya showed that the disease imposes substantial economic costs, jeopardizing the achievement of sustainable development goals (SDGs).[52] While global malaria mortality predominantly affects young children, clinical malaria affects all age groups throughout life. Malaria not only threatens health but also child education and adult productivity while burdening government budgets and economic development. Increased investments in malaria control can contribute to reducing this burden.[53]

Post-malaria syndrome

Post-malaria neurological syndrome (PMNS) is a disabling complication of malaria. The overall incidence is not known due to frequent misdiagnosis and under-reporting. Pathogenesis is not fully understood, but rapid response to immune-modulating treatment, along with similarities to autoimmune neurological disease, strongly supports a deregulated immunological genesis of this condition.[54] It is characterized by a myriad of neuropsychiatric manifestations, including mild neurological deficit to severe encephalopathy.[55]

PMNS should be considered in patients with neurological symptoms occurring within two months of cured acute disease, in which blood smears for malaria are negative and other etiologies have been ruled out.[56] As for the treatment, in most cases, the disease is self-limited, while in severe cases, corticosteroid therapy should be prescribed with a favorable outcome.[56] In one of the findings of a case report, the author encountered a case of a 60-year-old Italian man presenting with confusion, language disturbances, and Parkinson-like syndrome 3 weeks after complete remission from severe *P. falciparum* cerebral malaria. Chemical and microbiological analysis revealed aseptic meningitis, diffuse encephalitis, and abnormal immune activation. A diagnosis of PMNS was finally formulated and successfully treated with a high dose of steroids. An autoimmune mechanism is the most corroborated pathogenic hypothesis. Overall, the majority of PMNS cases revert without specific treatment. In most severe forms, high-dose steroids, intravenous immunoglobulins, and plasmapheresis have been shown to improve symptoms.[54]

Table 3: Long-term outcomes and sequelae in survivors.

Key findings	Outcomes	Considerations	References.
Cognitive and developmental delays	Motor, communication, and personal social delay.	Ischemic neuronal injury.	1, 4
Chronic organ dysfunction	Liver, RBCs, eyesight, and kidney problems	Urea, creatinine, hepatic enzymes, and markers.	8, 9
Cardiovascular health	Myocarditis and acute coronary syndrome	Cardiac biomarkers, ECG, and echo.	12
Psychosocial and economic impacts	Jeopardizing SDGs	Burden for budgets and economic loss.	16, 17
Post-malaria syndrome	Neuropsychiatric manifestations	Corticosteroid therapy for favorable outcomes	19, 20

Research gaps and future directions

Traditional diagnostic methods like microscopy and rapid tests cannot detect low-level infections accurately.[57] New biomarker research provides faster, more accurate, and easier ways to detect malaria.[57] These advancements are important for the early detection and effective treatment of malaria and have been shown to help reduce malaria worldwide, especially in high-resource areas.[57] These include the use of next-generation sequencing, proteomics, and metabolomics.[57] These biomarkers can be detected in blood, saliva, or urine, which makes screening less invasive and easier.[57] Using machine learning (ML) with biomarker data makes the diagnosis of malaria more accurate.[57] This can help identify different stages of infection and also detect drug-resistant strains.[57]

Creating multi-biomarker panels and portable devices can help with the detection of malaria in the future (Table 4).[57] Smartphone technologies and wearable sensors will allow real-time monitoring and diagnostics even in limited-resource areas.[57] The identification of a predictive immune signature for malaria immunity is important. A study found that if antibody responses are measured to a few specific antigens, the responses can accurately predict a person's immune status.[58] Therefore, it identifies the role of early intervention and helps in monitoring the effectiveness of vaccinations.[58] There is ongoing research to develop biomarkers to guide immunotherapy for critical illnesses like sepsis.[59] These efforts are ongoing and showing promising results in improving patient outcomes.[59]

Immunomodulation provides promising treatments.[60] It works by targeting different parts of the immune system.[60] The goal is to balance and slow down disease progression.[60] Although it's challenging to design safe and effective compounds, immunomodulation is still seen as a viable therapy.[60] It can be used alone or alongside other treatments.[60] It has potential applications in severe malaria and other infectious diseases (Table 4).[61]

Recognizing immune signatures that indicate malaria immunity can help in vaccine development.[58] By understanding which immune responses offer protection, researchers can create vaccines to effectively prevent severe malaria.[58] This is especially important for protecting vulnerable children.

Longitudinal studies are important for understanding the outcomes of severe malaria and immune imbalance. These studies show the progression of disease and can also help to assess the effectiveness of treatments.[62] This information is important for improving treatment strategies and patient care. Global studies on the long-term effects of severe malaria in children are important to conduct for developing effective public health strategies. These studies can help identify risk factors, inform policy decisions, and guide resource allocation.[63] The goal is to reduce the burden of malaria in children (Table 4).

Table 4: Research gaps and future directions.

Area	Current gap	Future direction	Potential impact
Diagnostics	Traditional microscopy and rapid tests miss low-level infections.	Develop biomarkers detectable in blood, saliva, or urine; next-gen sequencing, proteomics, metabolomics.	Faster, more accurate, and non-invasive malaria detection; early diagnosis improves outcomes.
Data integration	Limited use of advanced analytics in diagnostics.	Apply machine learning to biomarker datasets.	Enhanced diagnostic accuracy; detection of infection stages and drug-resistant strains.
Multi-biomarker panels	Reliance on single biomarkers limits diagnostic sensitivity.	Create multi-marker panels and portable detection devices.	Broader and more reliable detection, especially for field use in resource-limited settings.
Real-time monitoring	Lack of real-time, portable diagnostic solutions.	Incorporate smartphone-based technologies and wearable sensors.	Enable continuous monitoring and immediate diagnostics in remote or underserved areas.
Immunity prediction	Difficulty in assessing immune status against malaria.	Identify predictive immune signatures through specific antibody responses.	Early intervention strategies; monitoring vaccine effectiveness.
Immunotherapy guidance	No validated biomarkers to direct immunotherapy in infectious diseases.	Develop biomarkers to guide immunomodulation treatments for conditions like sepsis and severe malaria.	Personalize treatments and improve outcomes in critical care settings.
Immunomodulation therapies	Challenges in designing safe and effective immune-targeting drugs.	Continue development of targeted immunomodulatory compounds.	Potential to balance immune response and slow disease progression, applicable in malaria and beyond.

CONCLUSION

Immune dysregulation in severe malaria, such as cytokine imbalance and endothelial dysfunction, causes immune system to overreact. This can worsen the disease and lead to severe symptoms like cerebral malaria and severe anemia, leading to organ dysfunction. To fill the research gaps in malaria and immune imbalance, a good approach that will include creating advanced diagnostic tools, targeted treatments, and thorough longitudinal studies is required. These efforts will improve the understanding

and management of these health challenges, leading to better outcomes for affected populations.

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