

Role of Interleukin-6, Tumor Necrosis Factor-Alpha, and C-Reactive Protein in Pregnant and Non-Pregnant Malaria Patients

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Abstract: *Malaria remains a significant public health concern, particularly in tropical and subtropical regions, where Plasmodium species cause substantial morbidity and mortality. Pregnant women are especially vulnerable to malaria because pregnancy-related immunological and physiological changes may influence parasite susceptibility, inflammatory responses, and disease severity.*

Inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP), play important roles in the host response to malaria infection. IL-6 regulates immune activation and stimulates hepatic acute-phase protein production, TNF- α contributes to inflammatory responses and parasite control but may also promote tissue injury when excessively expressed, and CRP serves as a nonspecific marker of systemic inflammation..

Keywords: Malaria, interleukin-6, tumor necrosis factor-alpha, C-reactive protein, pregnancy, placental malaria, inflammatory biomarkers, maternal health.

I. INTRODUCTION

Malaria is an infectious disease caused by protozoan parasites of the genus Plasmodium and transmitted primarily through the bites of infected female Anopheles mosquitoes. The disease continues to pose a major challenge to global health, particularly in sub-Saharan Africa and parts of Asia. Clinical manifestations range from uncomplicated fever and chills to severe anaemia, respiratory distress, organ dysfunction, and death. The host immune response is essential for controlling parasite multiplication, but excessive or poorly regulated inflammation can contribute to disease pathology. Understanding the relationship between parasite infection and inflammatory mediators is therefore important for explaining differences in disease severity among patients.

Pregnancy introduces additional complexity into malaria pathogenesis. Changes in maternal immunity, placental physiology, and circulating blood volume may influence the clinical presentation and consequences of infection. In particular, Plasmodium falciparum can express parasite proteins that facilitate the sequestration of infected erythrocytes within the placenta. This process may lead to placental inflammation, impaired nutrient exchange, maternal anaemia, fetal growth restriction, low birth weight, and preterm delivery. Pregnant women, especially those experiencing their first or second pregnancy in malaria-endemic settings, may have increased susceptibility to placental infection because protective immunity against placental-binding parasite variants develops through repeated exposure.

Cytokines and acute-phase proteins provide useful insights into these host responses. IL-6 is a multifunctional cytokine involved in immune regulation, fever, acute-phase responses, and the activation of several immune-cell populations. TNF- α is a pro-inflammatory cytokine associated with parasite control, endothelial activation, fever, and inflammatory tissue injury. CRP is an acute-phase protein produced predominantly by the liver in response to inflammatory signals,

particularly IL-6. Measuring these biomarkers may help researchers characterize the inflammatory response associated with malaria and explore differences between pregnant and non-pregnant populations.

Nevertheless, biomarker concentrations are influenced by multiple factors, including the timing of sample collection, parasitaemia, concurrent infections, nutritional status, gestational age, and previous antimalarial treatment. Consequently, the interpretation of IL-6, TNF- α , and CRP requires careful consideration of both pregnancy status and the clinical context. This review synthesizes their biological functions, potential clinical relevance, and limitations as indicators of malaria-associated inflammation.

BIOLOGICAL ROLE OF INFLAMMATORY BIOMARKERS IN MALARIA

INTERLEUKIN-6 (IL-6)

Interleukin-6 is a multifunctional cytokine secreted by monocytes, macrophages, endothelial cells, and other immune and tissue cells in response to infection or tissue damage. During malaria, parasite-derived components stimulate innate immune receptors, activating signalling pathways that promote cytokine production. IL-6 contributes to fever, immune-cell regulation, hepatic acute-phase protein synthesis, and the coordination of inflammatory responses. Its concentration may increase with disease severity, although the magnitude of the increase differs across studies and patient populations.

A systematic review and meta-analysis published in Scientific Reports reported higher IL-6 concentrations among patients with malaria, particularly in those with severe disease. However, substantial heterogeneity between studies limits the use of a single IL-6 threshold for predicting severity.

In pregnant patients, IL-6 may reflect systemic inflammation as well as inflammatory activity at the maternal-placental interface. Placental malaria can involve the accumulation of infected erythrocytes and immune cells within placental blood spaces, potentially altering cytokine production. Nevertheless, IL-6 concentrations are also influenced by gestational stage, other infections, and pregnancy-related inflammatory conditions. Therefore, elevated IL-6 should be interpreted as evidence of an inflammatory response rather than definitive proof of placental malaria or severe infection.

TUMOR NECROSIS FACTOR-ALPHA (TNF- α)

TNF- α is a potent pro-inflammatory cytokine produced primarily by activated macrophages and monocytes, although other cells can also contribute. It participates in innate immune defence, endothelial activation, fever, leukocyte recruitment, and the regulation of immune responses against intracellular pathogens. During malaria infection, TNF- α may contribute to parasite control by activating immune mechanisms and coordinating inflammatory responses.

However, excessive TNF- α activity may also contribute to endothelial dysfunction, metabolic disturbances, tissue injury, and systemic inflammation. Its effects depend on the intensity and duration of the response, the anatomical site of cytokine production, and the balance between pro-inflammatory and regulatory mediators.

In pregnancy-associated malaria, TNF- α is particularly relevant because placental inflammation can interfere with normal placental function. Studies of placental malaria have reported elevated TNF-related inflammatory activity in infected women, although the magnitude and distribution of these changes vary according to parity, infection characteristics, and whether maternal peripheral or placental blood is examined.

TNF- α is consequently a valuable research marker for investigating malaria-associated inflammation. Nevertheless, an elevated concentration alone cannot establish disease severity, predict an adverse pregnancy outcome, or distinguish malaria from other inflammatory disorders.

C-REACTIVE PROTEIN (CRP)

C-reactive protein is an acute-phase protein produced mainly by hepatocytes in response to inflammatory signalling, particularly IL-6. Its concentration increases during many bacterial and viral infections, parasitic diseases, and

inflammatory tissue conditions. CRP binds to selected molecular structures, participates in complement-related immune processes, and contributes to the recognition and clearance of damaged cells and certain microbial components.

In malaria, elevated CRP may reflect the systemic inflammatory response associated with parasite infection. Concentrations may be higher in patients with complicated disease than in those with uncomplicated infection, but the relationship is not uniform. CRP is influenced by infection duration, disease severity, concurrent infections, liver function, and the timing of sample collection.

During pregnancy, CRP interpretation requires additional caution because its concentration may also be affected by gestational age, obesity, obstetric complications, and other inflammatory conditions. CRP is not specific to malaria and cannot independently confirm parasitaemia or identify placental sequestration. Its principal research value lies in providing a readily measurable indicator of systemic inflammation that can be interpreted alongside cytokines, parasite density, clinical findings, and pregnancy outcomes.

COMPARISON BETWEEN PREGNANT AND NON-PREGNANT MALARIA PATIENTS

Pregnant and non-pregnant malaria patients may exhibit different inflammatory profiles because pregnancy modifies immune regulation, circulating blood volume, endocrine activity, and the physiological environment in which infection occurs. These differences do not mean that every pregnant patient will have higher cytokine concentrations than every non-pregnant patient. Rather, they suggest that pregnancy status should be considered when comparing biomarker measurements.

In non-pregnant patients, circulating IL-6, TNF- α , and CRP may primarily reflect the systemic response to parasite burden, disease duration, and the severity of infection, alongside other host characteristics. In pregnant patients, these same systemic processes may coexist with placental sequestration and localized inflammation, particularly in *P. falciparum* infection.

A systematic review of biomarkers in placental malaria found that inflammatory markers were frequently investigated, but their diagnostic specificity remained limited. The review also highlighted that many studies collected samples only at delivery, restricting the ability to establish whether biomarkers could predict placental malaria earlier in pregnancy.

A meaningful comparison should therefore include pregnant malaria-positive patients, non-pregnant malaria-positive patients, and suitable uninfected comparison groups. Pregnant controls should ideally be matched or adjusted for gestational age, while non-pregnant controls should be comparable in age and relevant clinical characteristics. Parasite species, parasite density, parity, nutritional status, anaemia, antimalarial treatment, and concurrent infections should also be considered.

Biomarker	Principal biological role	Potential significance in malaria	Pregnancy-specific consideration	Main limitation
IL-6	Immune regulation and acute-phase response	May reflect systemic inflammation and disease severity	May be influenced by placental inflammation and gestational changes	Highly variable; no universally validated malaria-specific threshold
TNF- α	Pro-inflammatory signalling and immune-cell activation	Associated with parasite-induced inflammation and, in some studies, severe disease	May reflect maternal and placental inflammatory activity	Excessive inflammation is not specific to malaria
CRP	Hepatic acute-phase protein response	Indicates systemic inflammatory activity	Interpretation may be affected by pregnancy-related and obstetric inflammation	Cannot identify the cause or location of inflammation
Combined assessment	Integrates different aspects of	May improve characterization of disease	May help researchers investigate maternal and	Requires validation in pregnancy-specific

	inflammation	when used with clinical and parasitological measures	placental patterns	disease	populations
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Source: Synthesis of the reviewed literature; the table presents biological interpretation rather than a validated clinical scoring system.

REVIEW OF PREVIOUS STUDIES

Previous research has investigated the relationship between inflammatory biomarkers, malaria infection, and pregnancy outcomes. The findings support the biological importance of IL-6, TNF- α , and CRP, but they also reveal limitations in the consistency and clinical applicability of available evidence.

Hashmi et al. (2023) conducted a systematic review and meta-analysis examining inflammatory biomarkers associated with malaria infection and disease severity. The authors reported significantly higher IL-6 and TNF- α levels in patients with complicated malaria in the pooled analyses. CRP was also frequently elevated in complicated cases. However, considerable between-study heterogeneity and the limited diagnostic specificity of individual biomarkers suggested that they should not be used as independent diagnostic tests.

An earlier systematic review of peripheral and placental biomarkers in women with placental malaria examined the potential of host inflammatory responses to assist in identifying placental infection. The findings suggested that TNF-related inflammatory activity could be elevated in placental malaria, but the lack of specificity and the limited availability of longitudinal observations restricted the predictive value of the biomarkers.

Okamgba et al. (2018) investigated differences in leukocyte and cytokine profiles between maternal peripheral and placental circulation. Their study included malaria-infected and uninfected pregnant and postpartum women. The investigation demonstrated the importance of considering the sampling site when interpreting cytokine concentrations, because peripheral blood and placental blood may reflect different immunological environments.

Research on maternal and fetal responses to placental malaria has also shown that inflammatory responses can differ according to parity and the compartment in which biomarkers are measured. These findings indicate that pregnancy history and the local placental immune environment should be included in the interpretation of maternal inflammatory profiles.

Collectively, these studies support further investigation of IL-6, TNF- α , and CRP as complementary indicators of malaria-associated inflammation. However, differences in study design, patient selection, laboratory methods, parasite species, and clinical severity make direct comparisons difficult. The evidence does not establish a universal biomarker pattern that reliably distinguishes pregnant from non-pregnant malaria patients.

RELATIONSHIP BETWEEN BIOMARKERS AND PREGNANCY OUTCOMES

Malaria during pregnancy is associated with several adverse maternal and fetal outcomes, including maternal anaemia, placental dysfunction, fetal growth restriction, low birth weight, preterm birth, and pregnancy loss. Inflammation is one of the mechanisms that may contribute to these complications, although the relationship between a particular circulating biomarker and an individual outcome is not always direct.

IL-6 may reflect inflammatory activation and stimulate hepatic acute-phase responses. TNF- α may influence endothelial activity, placental inflammatory processes, and tissue function. CRP may provide a broader indication of the systemic acute-phase response. These pathways are biologically plausible links between infection and pregnancy complications, but biomarker elevation does not necessarily demonstrate that a mediator directly caused an adverse outcome.

A study examining systemic inflammatory responses to malaria during pregnancy evaluated associations between inflammatory mediators and pregnancy loss or preterm delivery. Its findings illustrate the complexity of these relationships: associations can differ according to the mediator, sample compartment, and statistical adjustment. Consequently, IL-6 and TNF- α should be evaluated alongside clinical and obstetric characteristics rather than treated as standalone prognostic markers.

Future studies should collect biomarker measurements at multiple gestational stages and follow pregnancies through delivery. Such designs would help determine whether early inflammatory changes predict subsequent complications or merely reflect infection at the time of testing.

CLINICAL SIGNIFICANCE OF BIOMARKER ASSESSMENT

The combined assessment of IL-6, TNF- α , and CRP may contribute to research on the host inflammatory response in malaria. Each marker provides somewhat different information: IL-6 reflects cytokine signalling and acute-phase activation, TNF- α represents a major component of pro-inflammatory signalling, and CRP reflects a downstream systemic response. Examining these markers together may therefore offer a broader picture of inflammation than measuring only one.

However, these biomarkers must not replace parasitological testing or established clinical assessment. Malaria diagnosis should rely on appropriate parasite-based testing, such as microscopy or a rapid diagnostic test, according to local clinical guidance. Biomarker results should be interpreted in the context of symptoms, parasite density where available, haemoglobin concentration, organ dysfunction, gestational age, and other possible causes of inflammation.

For pregnant patients, biomarker research may eventually help clarify differences between systemic infection and placental inflammatory processes. Nevertheless, routine clinical use for diagnosing placental malaria or predicting maternal and fetal outcomes requires further validation in appropriately designed studies.

Several research gaps remain. First, relatively few studies directly compare pregnant and non-pregnant malaria patients using the same sampling procedures, laboratory assays, and clinical definitions. This limits the ability to determine whether observed differences are attributable to pregnancy itself or to other patient characteristics.

Second, many studies use cross-sectional designs or collect samples at delivery. Longitudinal studies beginning early in pregnancy are needed to establish the temporal relationship between biomarker concentrations, infection episodes, treatment, and pregnancy outcomes.

Third, studies should distinguish between *P. falciparum*, *P. vivax*, and other relevant *Plasmodium* infections rather than assuming that their inflammatory patterns are identical. Differences in parasite biology and placental involvement may influence the interpretation of biomarkers.

Fourth, researchers should standardize sample handling, assay platforms, reporting units, and the timing of blood collection. Confounding variables—including parity, gestational age, parasite density, anaemia, nutrition, concurrent infection, and antimalarial treatment—should be measured and considered in statistical analyses.

Finally, predictive models combining inflammatory biomarkers with clinical and parasitological variables should be developed and externally validated. Researchers should report sensitivity, specificity, predictive values, calibration, and clinical utility rather than relying solely on statistically significant differences in biomarker concentrations.

The available literature has several limitations. First, studies differ in sample size, geographical setting, parasite species, infection severity, and participant characteristics. Second, cytokine concentrations may vary according to assay technology, specimen type, sample storage, and timing of collection. Third, some studies include only women at delivery, limiting conclusions about early pregnancy and the predictive value of inflammatory biomarkers. Fourth, elevated IL-6, TNF- α , and CRP can occur in multiple infectious and non-infectious conditions, which reduces their specificity for malaria. Finally, observational associations do not establish causation. These limitations indicate that the biomarkers should be interpreted cautiously and that further standardized, longitudinal investigations are necessary.

II. CONCLUSION

IL-6, TNF- α , and CRP are important components of the inflammatory response associated with malaria infection. IL-6 participates in immune regulation and acute-phase activation, TNF- α contributes to pro-inflammatory signalling and parasite-related immune responses, and CRP reflects systemic inflammatory activity. Evidence from systematic reviews and clinical studies indicates that these biomarkers are often elevated in complicated malaria, although findings vary between populations and studies.

Pregnant malaria patients require particular consideration because pregnancy-related immune changes and placental sequestration, especially in *P. falciparum* infection, may modify the distribution and intensity of inflammation. These processes may be associated with maternal anaemia, placental dysfunction, fetal growth restriction, and other adverse pregnancy outcomes. However, the available evidence does not establish that all three biomarkers consistently increase in every infected pregnant patient or that any single marker can reliably distinguish pregnant from non-pregnant malaria patients.

The combined evaluation of IL-6, TNF- α , and CRP may provide valuable information for understanding malaria-associated inflammation, but these markers should be interpreted alongside parasitological findings and clinical characteristics. Future research should prioritize direct comparisons between pregnant and non-pregnant patients, repeated measurements throughout pregnancy, standardized laboratory methods, and rigorous assessment of diagnostic and prognostic performance. Such evidence may clarify the clinical relevance of these biomarkers and improve understanding of the mechanisms connecting malaria infection, maternal inflammation, and pregnancy outcomes.

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