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Immune Biomarkers Predictive of Severe Malaria Progression Across Pediatric and Adult Cohorts

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ABSTRACT

Severe malaria, predominantly caused by Plasmodium falciparum, progresses unpredictably from uncomplicated infection to life-threatening complications, including cerebral malaria, severe anemia, and metabolic acidosis. Immune responses varied substantially between pediatric and adult populations, influencing disease trajectory and clinical outcomes. Identification of reliable immune biomarkers capable of predicting progression to severe disease remains a critical unmet need for early intervention strategies. This review synthesized current evidence on immune biomarkers that predict severe malaria progression, evaluating their performance across pediatric and adult cohorts while examining age-dependent immunological differences that modulate predictive capacity. A comprehensive analysis of literature examining soluble immune mediators, cellular markers, and functional immune parameters associated with severe malaria progression in diverse age groups was conducted. Elevated cytokines, including tumor necrosis factor alpha, interleukin 6, and interleukin 10, demonstrated prognostic value but showed variable performance across age groups. Thrombocytopenia and parasite biomass markers, including plasma histidine-rich protein 2 provided complementary prognostic information. Pediatric cohorts exhibited distinct immunological profiles characterized by innate immune predominance and limited regulatory responses, while adults demonstrated enhanced adaptive immunity but increased immunopathology. Functional assays measuring phagocytic capacity and antibody-dependent cellular responses showed promise but required standardization. Most studies demonstrated methodological limitations, including small sample sizes, single time point assessments, and inadequate validation across diverse transmission settings. Immune biomarker panels incorporating endothelial dysfunction markers, inflammatory cytokines, and parasite burden indicators offered potential for risk stratification, though age-specific thresholds and validation in prospective clinical trials remain essential for clinical implementation.

Keywords: Severe malaria, Immune biomarkers, Cytokines, Endothelial activation, Age-dependent immunity

INTRODUCTION

Immune responses to Plasmodium falciparum infection involve coordinated activation of innate and adaptive immune mechanisms that determine whether infection is controlled, progresses to uncomplicated malaria, or advances to severe life-threatening disease [1, 2]. Upon invasion of erythrocytes, parasites release pathogen-associated molecular patterns, including glycosylphosphatidylinositol anchors, hemozoin crystals, and parasite DNA that engage toll-like receptors on immune cells, triggering inflammatory cascades [3]. Pro-inflammatory cytokines such as tumor necrosis factor alpha and interferon gamma facilitate parasite clearance through enhanced phagocytosis and nitric oxide production, but simultaneously contribute to immunopathology when dysregulated. Counter-regulatory responses mediated by interleukin 10 and transforming growth factor beta attempt to limit excessive inflammation, yet may impair effective parasite control [4]. Endothelial activation constitutes a critical component of pathogenesis, with infected erythrocyte sequestration inducing vascular dysfunction, increased permeability, and microcirculatory obstruction. Antibody responses targeting merozoite surface proteins and variant surface antigens gradually develop following repeated exposures, conferring partial protection in endemic populations. Cellular immune responses involving CD4 and CD8 T lymphocytes contribute to both parasite clearance and tissue damage, depending on activation phenotypes and regulatory mechanisms [5, 6].

The transition from uncomplicated to severe malaria involves complex interactions between parasite virulence factors, host immune responses, and organ-specific pathophysiology. Severe manifestations, including cerebral malaria, severe malarial anemia, respiratory distress, and metabolic acidosis, result from distinct but overlapping pathogenic mechanisms. Cerebral malaria pathogenesis involves sequestration of infected erythrocytes in the brain microvasculature, local inflammatory responses, blood-brain barrier disruption, and edema formation [7, 8]. Severe anemia develops through hemolysis of parasitized and uninfected erythrocytes, dyserythropoiesis, and splenic sequestration. Age profoundly influences disease manifestation patterns, with young children in endemic areas predominantly developing severe anemia, while older children experience cerebral malaria, and adults exhibit multi-organ dysfunction. These age-dependent differences reflect cumulative malaria exposure, partial immunity acquisition, and developmental maturation of immune regulatory mechanisms. Semi-immune adults in endemic regions typically experience uncomplicated disease, whereas malaria-naive adults demonstrate increased susceptibility to severe complications. Pregnant women constitute a high-risk group due to placental sequestration and altered immune responses. This review critically evaluates immune biomarkers that predict severe malaria progression in pediatric and adult populations, examining age-related immunological differences influencing biomarker performance and clinical utility.

Cytokine Profiles and Inflammatory Mediators as Prognostic Indicators

Cytokine dysregulation represents a hallmark of severe malaria pathogenesis, with excessive pro-inflammatory responses contributing to vascular dysfunction and organ damage while inadequate responses permit uncontrolled parasitemia [9]. Tumor necrosis factor alpha demonstrates consistently elevated concentrations in patients progressing to severe disease compared to uncomplicated malaria, with levels correlating with mortality risk across multiple studies. Mechanistically, tumor necrosis factor alpha enhances endothelial adhesion molecule expression, promotes microvascular permeability, and induces metabolic derangements, including hypoglycemia and lactic acidosis [10]. However, prognostic thresholds vary substantially across populations, with pediatric cohorts generally exhibiting lower absolute concentrations than adults for equivalent disease severity. Interleukin 6 elevation precedes clinical deterioration in longitudinal studies, suggesting potential utility for early intervention targeting, though considerable overlap exists between uncomplicated and severe cases, limiting discriminatory capacity. Interleukin 10, traditionally considered anti-inflammatory, demonstrates paradoxical associations with severity, with very high concentrations indicating failure of immune regulation and predicting poor outcomes in some cohorts but showing protective associations in others.

The balance between pro-inflammatory and regulatory cytokines provides superior prognostic information compared to individual mediators, with elevated tumor necrosis factor alpha to interleukin 10 ratios consistently associating with progression in pediatric African cohorts. Chemokines, including CXCL10, CCL2, and CCL5, reflect immune cell recruitment and activation, demonstrating associations with cerebral malaria and respiratory complications [11]. Age-dependent differences in cytokine responses reflect developmental immune maturation, with neonates and young infants exhibiting blunted tumor necrosis factor alpha responses associated with reduced severe disease risk during early life. Conversely, older children demonstrate robust inflammatory responses that contribute to cerebral malaria pathogenesis. Adult non-immune individuals mount excessive inflammatory responses comparable to pediatric patients, while semi-immune adults exhibit controlled cytokine elevation with enhanced regulatory mechanisms [12, 13]. Methodological challenges complicate cytokine biomarker interpretation, including sample timing relative to symptom onset, antibiotic pre-treatment effects, concurrent infections, and storage conditions affecting protein stability. Multiplex assays enable comprehensive cytokine profiling but require careful validation and standardization across laboratories. Despite extensive investigation, no single cytokine biomarker achieves sufficient sensitivity and specificity for clinical decision making, necessitating multiparameter approaches combining inflammatory mediators with complementary biomarkers reflecting distinct pathogenic pathways.

Endothelial Activation Markers and Microvascular Dysfunction Indicators

Endothelial dysfunction constitutes a central pathogenic mechanism in severe malaria, with sequestration of parasitized erythrocytes triggering vascular activation, increased permeability, and microcirculatory obstruction leading to tissue hypoxia and organ dysfunction [14]. Angiopoietin 2, a peptide hormone regulating endothelial quiescence and vascular stability, emerges as one of the most robust prognostic biomarkers across diverse populations and age groups [15]. Elevated angiopoietin 2 concentrations predict mortality in both pediatric and adult severe malaria cohorts, with area under receiver operating characteristic curves consistently exceeding 0.80 across multiple validation studies. Mechanistically, angiopoietin 2 antagonizes angiopoietin 1-mediated Tie2 receptor activation, destabilizing endothelial cell junctions and promoting vascular leak. Parasite products and inflammatory mediators induce endothelial angiopoietin 2 release, creating a pathogenic cascade amplifying vascular dysfunction. Longitudinal measurements demonstrate that angiopoietin 2 elevation precedes clinical deterioration, providing a window for therapeutic intervention, though optimal timing and threshold values require further validation.

Soluble intercellular adhesion molecule 1 reflects endothelial activation and mediates cytoadherence of infected erythrocytes expressing PfEMP1 variants, demonstrating elevated concentrations in severe malaria, particularly cerebral manifestations [16, 17]. However, intercellular adhesion molecule 1 shows greater variability in prognostic performance across studies compared to angiopoiesin 2, potentially reflecting diverse PfEMP1 binding phenotypes and genetic variation in ICAM1 polymorphisms affecting receptor expression and function. Von Willebrand factor, a marker of endothelial perturbation and coagulation activation, associates with disease severity and mortality risk, with ultra-large multimers indicating reduced ADAMTS13 activity and increased thrombotic risk. Thrombomodulin and endothelial protein C receptor, components of the protein C anticoagulant pathway, demonstrate altered expression in severe malaria, contributing to coagulopathy and microvascular thrombosis [18, 19]. Syndecan 1 and hyaluronan elevation indicate glycocalyx degradation, a recently recognized component of endothelial dysfunction associated with increased vascular permeability and organ dysfunction in both pediatric and adult cohorts. Age-related differences in endothelial marker performance appear less pronounced than for cytokine biomarkers, with angiopoietin 2 showing consistent prognostic value across age groups. However, baseline endothelial activation states differ between populations, with chronic infections and nutritional status influencing marker concentrations. Combining endothelial markers with parasite biomass indicators improves risk stratification, suggesting complementary pathogenic contributions requiring integrated assessment for optimal prognostic accuracy.

Parasite Biomass Quantification and Sequestration Biomarkers

Accurate assessment of total parasite biomass, including both circulating and sequestered forms, provides critical prognostic information beyond peripheral parasitemia measured through microscopy. Histidine-rich protein 2, a water-soluble protein abundantly expressed by Plasmodium falciparum trophozoites and schizonts, demonstrates superior correlation with total parasite burden compared to microscopic parasite counts, as circulating concentrations reflect both peripheral and sequestered parasites [20, 21]. Plasma histidine-rich protein 2 concentrations predict severe disease and mortality across pediatric and adult populations, with quantitative assays demonstrating dose-response relationships. However, histidine-rich protein 2 gene deletions, increasingly prevalent in some African and South American regions, preclude biomarker utility in affected areas and complicate rapid diagnostic test performance. Parasite lactate dehydrogenase, another parasite-specific enzyme detectable in plasma, provides an alternative biomass marker, though generally showing lower concentrations and reduced sensitivity compared to histidine-rich protein 2.

Circulating parasite DNA quantification through quantitative polymerase chain reaction offers precise biomass assessment, demonstrating superior sensitivity to microscopy and correlation with disease severity [22]. Parasite nucleic acid levels predict treatment response and resolution kinetics, providing pharmacodynamic endpoints for antimalarial efficacy assessment. However, technical complexity and cost limit implementation in resource-constrained settings where malaria burden is greatest. Cell-free hemoglobin and haptoglobin depletion reflect intravascular hemolysis severity, indirectly indicating parasite biomass and contributing independently to pathogenesis through nitric oxide scavenging, oxidative stress, and heme-mediated inflammation. These hemolysis markers show particular relevance for severe anemia prediction in pediatric cohorts where anemia constitutes a predominant manifestation. Age-dependent differences in parasite biomass associations with severity reflect acquired immunity, with equivalent peripheral parasitemia producing different clinical outcomes across age groups due to variable antibody-mediated sequestration patterns and cytoadherence phenotypes.

Rosetting capacity and cytoadherence phenotypes of parasite isolates, assessed through specialized binding assays, predict cerebral malaria risk, though requiring fresh samples and specialized laboratory capacity, limiting clinical utility [23]. PfEMP1 variant expression profiling through quantitative transcriptional analysis reveals that parasites expressing specific binding domains associate with severe disease, providing mechanistic insights, though lacking practical bedside applicability. Integration of parasite biomass markers with immune and endothelial biomarkers captures complementary pathogenic dimensions, with high parasite burden combined with elevated angiopoietin 2 or inflammatory cytokines identifying the highest risk patients across age groups. Standardization of measurement platforms, establishment of age-specific reference ranges, and validation in diverse transmission settings remain essential for clinical implementation of parasite biomass biomarkers in prognostic algorithms.

Cellular Immune Markers and Functional Immune Assays

Beyond soluble mediators, cellular immune profiles and functional capacity assessments provide insights into protective versus pathogenic immune responses predicting disease trajectory. Thrombocytopenia consistently associates with severe malaria across age groups, reflecting platelet consumption through sequestration, immune-mediated destruction, and direct parasite interactions [24]. Platelet counts below 50,000 cells per microliter predict increased mortality risk, with severe thrombocytopenia indicating disseminated intravascular coagulation and multi-organ dysfunction. However, thrombocytopenia occurs commonly in uncomplicated malaria, limiting specificity as an isolated prognostic marker. Monocyte and neutrophil activation states, assessed through surface marker expression of CD16, CD64, and HLA DR, differentiate disease severity, with activated phenotypes associating with

worse outcomes but showing substantial overlap across clinical categories [25, 26]. Regulatory T cell frequencies demonstrate inverse associations with disease severity in some studies, suggesting protective roles through inflammation limitation, while other investigations document elevated regulatory populations in severe cases, potentially impairing effective parasite clearance.

Functional assays measuring phagocytic capacity of monocytes and neutrophils for infected erythrocytes and free merozoites demonstrate reduced activity in severe disease despite cellular activation, suggesting functional exhaustion [27, 28]. Antibody-dependent cellular cytotoxicity and antibody-dependent respiratory burst assays quantify opsonic antibody functionality, with reduced activity predicting disease progression in longitudinal cohorts. These functional assessments capture integrated immune competence beyond static biomarker measurements, though technical complexity and requirement for fresh samples limit implementation. Age profoundly influences cellular immune profiles, with neonates and young infants exhibiting immature neutrophil and monocyte responses but reduced inflammatory pathology. Children in endemic areas develop memory T cell and B cell populations recognizing parasite antigens, though responses remain incomplete compared to adults [29]. Flow cytometric immune phenotyping studies reveal age-dependent shifts in T cell subset distributions, with younger children showing higher proportions of naive cells and limited regulatory populations compared to adults.

Recent investigations employing high-dimensional immune profiling through mass cytometry and transcriptomics identify distinct immune signatures associated with severe disease across age groups. These approaches reveal previously unappreciated immune cell populations and activation states contributing to pathogenesis or protection. However, translating complex multiparameter immune signatures into clinically applicable biomarkers requires dimensionality reduction, validation in independent cohorts, and development of simplified measurement platforms. The dynamic nature of immune responses during infection necessitates longitudinal sampling to capture temporal evolution, with baseline and early response markers potentially offering superior predictive value compared to measurements at clinical presentation when pathogenic processes are advanced. Integration of cellular markers with soluble mediators and parasite parameters within machine learning algorithms shows promise for developing robust prognostic models, though clinical validation and regulatory approval pathways remain to be established.

Age-Dependent Immunological Differences and Implications for Biomarker Interpretation

Age related immunological differences fundamentally influence biomarker performance and interpretation, reflecting developmental maturation, cumulative pathogen exposure, and acquisition of malaria-specific immunity [30]. Neonates and young infants demonstrate relative protection from severe malaria despite limited adaptive immunity, attributed to maternal antibody transfer, fetal hemoglobin presence, and unique cytokine profiles characterized by elevated interleukin 10 and reduced tumor necrosis factor alpha responses, dampening immunopathology [31]. As maternal antibody wanes during the first six months, vulnerability increases, coinciding with immune system maturation toward pro-inflammatory phenotypes. Children aged one to five years in endemic areas experience the highest severe malaria incidence, particularly cerebral malaria and severe anemia, reflecting insufficient acquired immunity combined with robust inflammatory capacity [32]. Biomarker studies in this age group demonstrate elevated cytokine concentrations and endothelial activation markers at presentation, with thresholds predicting mortality differing from adult values.

Older children and adolescents in endemic settings develop partial immunity through repeated exposures, characterized by anti-parasite antibodies targeting merozoite surface proteins, apical membrane antigen 1, and variant surface antigens, plus memory T cell responses enabling rapid parasite control [33]. These individuals tolerate higher parasitemias without progression to severe disease, complicating biomarker interpretation as absolute parasite biomass shows reduced prognostic value compared to younger children. However, breakthrough severe cases in this age group demonstrate distinct immune profiles, suggesting specific immunological deficits or exposure to novel parasite variants evading acquired immunity. Adults in endemic areas with substantial previous exposure typically experience uncomplicated malaria or asymptomatic parasitemia, with severe disease occurring primarily during pregnancy, immunosuppression, or prolonged absence from endemic areas with immunity waning. Biomarker profiles in semi-immune adults show controlled inflammatory responses, efficient parasite clearance, and limited endothelial dysfunction compared to non-immune adults or children [34].

Non-immune adults, including travelers and individuals in low transmission settings experiencing initial malaria infections, demonstrate pathophysiology resembling pediatric severe malaria with excessive inflammatory responses, pronounced endothelial activation, and rapid progression to organ dysfunction [35]. These individuals require distinct prognostic thresholds and risk assessment algorithms compared to endemic populations. Pregnancy induces specific immune alterations, including CD4 T cell responses and altered cytokine profiles, with primigravidae demonstrating the greatest vulnerability due to limited immunity to placental binding parasite variants [36]. Nutritional status, concurrent infections including helminth co-infections and HIV, genetic factors such as hemoglobin variants and G6PD deficiency, and seasonal transmission patterns introduce additional complexity to biomarker interpretation across age groups. Comprehensive prognostic models must incorporate age, transmission intensity, pregnancy status, and comorbidities alongside immune biomarkers for optimal performance.

Future research should focus on age-stratified biomarker validation, mechanistic investigations explaining age-dependent immunological differences, and the development of practical point-of-care assays enabling biomarker-guided clinical decisions in resource-limited settings where severe malaria burden is greatest.

CONCLUSION

Immune biomarkers demonstrate substantial potential for predicting severe malaria progression, with endothelial activation markers, inflammatory cytokines, and parasite biomass indicators showing consistent associations across diverse populations. Angiopoietin 2 emerges as the most robust single biomarker, demonstrating prognostic value across pediatric and adult cohorts, though optimal thresholds require age stratification and validation in prospective clinical trials. Cytokine profiles, particularly tumor necrosis factor alpha, interleukin 6, and interleukin 10, provide complementary information, though exhibiting greater variability across age groups and transmission settings. Parasite biomass markers, including histidine-rich protein 2 quantification, offer superior assessment of total parasite burden compared to peripheral parasitemia, though gene deletions limit applicability in some regions. Cellular immune markers and functional assays capture immune competence but require methodological standardization for clinical implementation. Age profoundly influences both disease manifestation patterns and immune biomarker profiles, necessitating age-specific reference ranges and prognostic algorithms. Evidence quality varies substantially, with many studies employing small sample sizes, single-center designs, and inadequate control for confounding factors, including nutritional status, concurrent infections, and prior antimalarial exposure. Most investigations utilize single-time point assessments at clinical presentation, missing opportunities to identify early biomarker changes enabling preemptive intervention. Multiparameter biomarker panels incorporating distinct pathogenic pathways show promise for superior prognostic accuracy, though requiring validation across diverse settings and integration into practical clinical decision tools suitable for resource-limited environments. Prospective multicenter studies should validate age-stratified multiparameter biomarker panels combining endothelial activation markers, inflammatory mediators, and parasite biomass quantification for early identification of patients at risk for severe malaria progression, enabling targeted intensive monitoring and adjunctive therapy evaluation.

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