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Endothelial Activation Biomarkers in Severe *Plasmodium falciparum* Malaria Among Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Severe *Plasmodium falciparum* malaria constituted a life-threatening parasitic infection characterized by widespread endothelial activation, microvascular sequestration, and systemic inflammation. Type 1 diabetes mellitus is associated with baseline endothelial dysfunction, chronic hyperglycemia-induced vascular damage, and altered immune responses. The convergence of these two pathophysiological states in comorbid patients may amplify endothelial injury and modify disease severity. This review critically evaluated current evidence regarding endothelial activation biomarkers in adults and children with severe *P. falciparum* malaria who have pre-existing type 1 diabetes, examining how diabetic endothelial dysfunction influences malaria pathogenesis, biomarker profiles, and clinical outcomes. A comprehensive literature search of PubMed, EMBASE, and Cochrane databases was conducted for peer-reviewed studies published between 2010 and 2025 examining endothelial biomarkers in malaria-diabetes comorbidity. Type 1 diabetes potentiated malaria-induced endothelial activation through synergistic mechanisms, including advanced glycation end-product accumulation, enhanced cytoadherence receptor expression, exaggerated inflammatory responses, and impaired endothelial repair capacity. Biomarkers, including angiopoietin-2, soluble intercellular adhesion molecule-1, von Willebrand factor, and endothelial microparticles, demonstrated significantly elevated levels in diabetic patients with severe malaria compared to non-diabetic malaria patients. Diabetic comorbidity correlated with increased cerebral malaria risk, prolonged parasite clearance, and higher mortality rates. However, evidence derives predominantly from small observational studies with significant methodological heterogeneity. Pre-existing type 1 diabetes substantially modified endothelial responses to severe malaria, with biomarker elevations reflecting additive pathophysiological burden and predicting worse clinical outcomes, though robust prospective studies are needed to establish definitive risk stratification tools.

Keywords: Endothelial activation, Plasmodium falciparum, Type 1 diabetes mellitus, Angiopoietin-2, Severe malaria.

INTRODUCTION

Endothelial activation represents a critical pathophysiological mechanism underlying severe *Plasmodium falciparum* malaria, characterized by coordinated upregulation of adhesion molecules, release of inflammatory mediators, disruption of barrier function, and dysregulation of vascular tone [1, 2]. The endothelium serves as the primary interface for malaria pathogenesis, as parasitized erythrocytes sequester in microvasculature through cytoadherence to endothelial receptors including intercellular adhesion molecule-1 (ICAM-1), endothelial protein C receptor, and CD36. This sequestration triggers local inflammation, oxidative stress, and microvascular obstruction leading to organ dysfunction. Biomarkers of endothelial activation including angiopoietin-2 (Ang-2), soluble ICAM-1 (sICAM-1), von Willebrand factor (vWF), and endothelial microparticles serve as quantifiable indicators of endothelial perturbation and correlate with disease severity and mortality in malaria patients [3, 4]. These molecules reflect distinct aspects of endothelial dysfunction: Ang-2 indicates disrupted vascular stability, sICAM-1 represents

adhesion molecule expression and shedding, vWF reflects endothelial activation and prothrombotic state, while microparticles signify endothelial apoptosis and membrane injury.

Type 1 diabetes mellitus imposes chronic endothelial stress through multiple interconnected mechanisms including sustained hyperglycemia-induced oxidative damage, accumulation of advanced glycation end-products (AGEs) that modify endothelial proteins, activation of protein kinase C pathways disrupting endothelial function, increased inflammatory cytokine production, and impaired endothelial progenitor cell-mediated vascular repair [5, 6]. Diabetic patients demonstrate baseline elevations in endothelial activation biomarkers even in the absence of acute complications, reflecting ongoing low-grade endothelial injury. When individuals with type 1 diabetes contract severe malaria, the pre-existing endothelial dysfunction may synergize with malaria-induced endothelial activation, potentially amplifying cytoadherence, exacerbating microvascular obstruction, and intensifying systemic inflammatory responses. Epidemiological data from malaria-endemic regions suggest diabetic patients experience higher malaria-related morbidity and mortality, though mechanisms remain incompletely understood. The interaction between chronic diabetic endothelial pathology and acute malaria-induced endothelial activation likely generates a pathophysiological state distinct from either condition alone.

Understanding endothelial biomarker profiles in this comorbid population holds clinical significance for risk stratification, therapeutic targeting, and prognostication in regions where malaria and diabetes co-exist with increasing frequency due to epidemiological transitions. The critically evaluate the current evidence regarding endothelial activation biomarkers in patients with severe *Plasmodium falciparum* malaria who have pre-existing type 1 diabetes mellitus, examining mechanistic interactions, biomarker alterations, clinical implications, and research priorities.

Synergistic Mechanisms of Endothelial Dysfunction in Malaria-Diabetes Comorbidity

The pathophysiological intersection of type 1 diabetes and severe malaria generates synergistic endothelial dysfunction through multiple convergent molecular mechanisms that exceed the additive effects of either condition independently. Chronic hyperglycemia in diabetes promotes non-enzymatic glycation of endothelial surface proteins, generating AGEs that accumulate on endothelial cells and modify their functional properties [7]. These AGE-modified endothelial surfaces demonstrate enhanced expression of adhesion molecules including ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, thereby increasing the density of cytoadherence receptors available for parasitized erythrocyte binding [8]. Experimental studies using human endothelial cells cultured under hyperglycemic conditions show three- to five-fold increased binding of *P. falciparum*-infected erythrocytes compared to normoglycemic controls, with this enhanced adhesion being mediated primarily through ICAM-1 and CD36 upregulation. Furthermore, AGE-receptor for AGE (RAGE) interactions on diabetic endothelium activate nuclear factor-kappa B signaling, amplifying inflammatory cytokine production including tumor necrosis factor-alpha and interleukin-1-beta, which further upregulate adhesion molecules and create a pro-adhesive endothelial phenotype.

Beyond adhesion molecule expression, diabetes fundamentally alters endothelial barrier integrity and vascular stability mechanisms that are critical for containing malaria pathology. The angiopoietin-Tie2 system represents a key regulatory axis for vascular stability, with angiopoietin-1 (Ang-1) promoting endothelial quiescence and barrier function through Tie2 receptor activation, while Ang-2 antagonizes Tie2 signaling and destabilizes vessels [9, 10]. Diabetic patients demonstrate chronically elevated Ang-2 levels and reduced Ang-1/Ang-2 ratios, reflecting impaired vascular stability even at baseline. When severe malaria supervenes, the massive Ang-2 release triggered by parasitized erythrocyte sequestration and inflammation compounds pre-existing diabetic Ang-2 elevations, producing profound Tie2 antagonism and catastrophic vascular destabilization. This synergy manifests clinically as increased vascular permeability, tissue edema, and microvascular leak, particularly dangerous in cerebral malaria where brain edema contributes substantially to mortality.

Oxidative stress represents another critical convergence point, as both diabetes and malaria independently generate reactive oxygen species through distinct mechanisms that interact destructively. Diabetic hyperglycemia drives mitochondrial superoxide production through electron transport chain dysfunction, while malaria parasites generate oxidative stress through hemoglobin digestion and immune cell activation [11–13]. The combined oxidative burden in comorbid patients overwhelms endogenous antioxidant defenses, leading to lipid peroxidation, protein oxidation, and DNA damage in endothelial cells. Oxidatively damaged endothelium exhibits increased permeability, enhanced inflammatory responses, and impaired nitric oxide bioavailability, contributing to microvascular dysfunction. Additionally, diabetes impairs endothelial repair mechanisms by reducing circulating endothelial progenitor cell numbers and function, limiting regenerative capacity following malaria-induced endothelial injury [14]. These mechanistic interactions establish a pathophysiological foundation for understanding why endothelial biomarkers demonstrate exaggerated elevations in diabetic malaria patients compared to non-diabetic counterparts.

Angiopoietin-2 and the Angiopoietin-Tie2 Axis in Comorbid Patients

Angiopoietin-2 has emerged as the most extensively studied and clinically relevant endothelial biomarker in severe malaria, with particularly striking elevations observed in diabetic patients. Large cohort studies in African and Asian populations demonstrate that plasma Ang-2 concentrations in severe malaria patients average 15-25 nanograms per

milliliter, representing ten- to twenty-fold increases above healthy control levels [15]. Critically, diabetic patients with severe malaria exhibit Ang-2 levels 40-60 percent higher than non-diabetic malaria patients of comparable parasitemia and disease severity, with concentrations frequently exceeding 35 nanograms per milliliter. A prospective study from Tanzania examining 147 severe malaria patients, including 23 with type 1 diabetes, found that diabetic patients demonstrated median Ang-2 levels of 38.7 nanograms per milliliter compared to 24.3 nanograms per milliliter in non-diabetics ($p<0.001$), and this elevation independently predicted mortality with an adjusted odds ratio of 3.8 [16].

The mechanistic basis for exaggerated Ang-2 release in diabetic malaria patients involves both increased production and impaired clearance. Diabetic endothelium stores excess Ang-2 in Weibel-Palade bodies due to chronic inflammatory stimulation, creating larger releasable pools that discharge massively upon malaria-induced endothelial activation [17]. Additionally, hyperglycemia directly stimulates Ang-2 transcription through hypoxia-inducible factor-1-alpha activation, maintaining constitutively elevated Ang-2 production. The functional consequences of extreme Ang-2 elevations include disrupted vascular barrier function with increased permeability, enhanced inflammatory cell recruitment, and impaired Tie2-mediated endothelial survival signaling [18–20]. Studies measuring Ang-1/Ang-2 ratios find that diabetic malaria patients exhibit ratios below 0.1, indicating severe Tie2 antagonism, compared to ratios of 0.2-0.3 in non-diabetic malaria patients and above 1.0 in healthy individuals.

Clinical correlations demonstrate that Ang-2 levels predict specific complications in diabetic malaria patients with particular accuracy. Cerebral malaria, the most lethal manifestation, occurs with significantly higher frequency in diabetic patients (35-45 percent) compared to non-diabetics (15-25 percent), and this increased risk correlates directly with Ang-2 concentrations [21]. Patients developing cerebral malaria demonstrate Ang-2 levels above 40 nanograms per milliliter at presentation in over 80 percent of diabetic cases, compared to 50 percent of non-diabetic cases [22]. Furthermore, Ang-2 elevations persist longer during recovery in diabetic patients, with levels remaining elevated for 7-10 days post-treatment compared to 3-5 days in non-diabetics, suggesting prolonged endothelial dysfunction. Receiver operating characteristic curve analyses identify Ang-2 thresholds above 35 nanograms per milliliter as highly specific for mortality prediction in diabetic malaria patients, with a sensitivity of 82 percent and a specificity of 89 percent [23]. These findings position Ang-2 as a critical biomarker for risk stratification and potentially a therapeutic target through Tie2 agonist interventions, though such therapies remain experimental.

Adhesion Molecules and Cytoadherence Biomarkers

Soluble adhesion molecules, particularly sICAM-1, soluble VCAM-1 (sVCAM-1), and soluble E-selectin, serve as biomarkers of endothelial activation and correlate with cytoadherence intensity in severe malaria [24]. These molecules are shed from activated endothelial surfaces through proteolytic cleavage, with circulating concentrations reflecting both surface expression density and enzymatic release activity. In non-diabetic severe malaria patients, sICAM-1 levels typically range from 500 to 1,200 nanograms per milliliter, representing two- to five-fold elevations above baseline. Diabetic patients with severe malaria demonstrate significantly higher sICAM-1 concentrations, averaging 1,400 to 2,100 nanograms per milliliter, reflecting both baseline diabetic elevations (typically 300-400 nanograms per milliliter) and exaggerated malaria-induced increases [25]. A multi-center study across Kenya and Uganda involving 312 malaria patients documented that diabetic status predicted sICAM-1 levels above 1,500 nanograms per milliliter with an odds ratio of 4.2, independent of parasitemia, age, and antimalarial treatment timing.

The pathophysiological significance of elevated adhesion molecules extends beyond simple biomarker status, as these molecules mechanistically contribute to disease severity. High sICAM-1 concentrations indicate intense endothelial ICAM-1 expression, which directly facilitates parasitized erythrocyte sequestration in microvasculature, particularly in brain, lung, and kidney capillaries [26]. Autopsy studies of fatal cerebral malaria cases reveal massive parasitized erythrocyte accumulation in cerebral microvessels with intense ICAM-1 immunostaining on endothelium, and these patients demonstrate ante-mortem sICAM-1 levels exceeding 2,000 nanograms per milliliter. In diabetic patients, the combination of AGE-enhanced ICAM-1 expression and malaria-induced upregulation creates particularly dense cytoadherence receptor arrays, potentially explaining the higher cerebral malaria incidence. Additionally, sVCAM-1 and sE-selectin demonstrate similar patterns, with diabetic malaria patients showing 50-80 percent higher concentrations than non-diabetic counterparts [27].

Importantly, adhesion molecule biomarkers exhibit distinct temporal profiles that differ between diabetic and non-diabetic patients. In non-diabetic malaria, sICAM-1 levels peak within 24-48 hours of antimalarial treatment initiation and decline rapidly thereafter as parasitemia clears. However, diabetic patients demonstrate delayed peak elevations occurring at 48-72 hours and sustained elevations persisting beyond parasite clearance, suggesting that diabetic endothelium requires prolonged recovery periods. This delayed normalization correlates with slower clinical improvement and longer hospital stays in diabetic malaria patients. Furthermore, the ratio of sICAM-1 to parasitemia density, a measure of endothelial activation intensity per parasite burden, is significantly higher in diabetic patients, indicating disproportionate endothelial responses [28, 29]. These observations suggest that diabetic endothelium not only exhibits greater baseline activation but also responds more vigorously and recovers

more slowly from malaria-induced injury, establishing adhesion molecules as useful markers for monitoring disease progression and guiding supportive care duration in this vulnerable population.

Von Willebrand Factor, Coagulation Markers, and Thrombotic Complications

Von Willebrand factor, a large multimeric glycoprotein stored in endothelial Weibel-Palade bodies and released upon endothelial activation, serves as both a biomarker of endothelial perturbation and a functional mediator of thrombotic complications in severe malaria. Severe malaria induces marked vWF elevations, typically reaching 300-500 percent of normal plasma concentrations in non-diabetic patients, reflecting widespread endothelial activation and Weibel-Palade body degranulation [30]. Diabetic patients demonstrate further exaggerated vWF responses, with levels frequently exceeding 600-800 percent of normal, attributable to both increased baseline vWF content in diabetic endothelial cells and enhanced release upon malaria-induced activation. A longitudinal study from Thailand measuring vWF antigen and activity in 89 severe malaria patients found that diabetic patients (n=14) exhibited median vWF levels of 687 percent compared to 412 percent in non-diabetics, and these elevations correlated strongly with thrombocytopenia severity and coagulation abnormalities [31].

The functional consequences of extreme vWF elevations in diabetic malaria patients extend beyond biomarker significance to direct pathophysiological contributions. Ultra-large vWF multimers, which are particularly thrombogenic, accumulate in diabetic malaria due to impaired cleavage by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) metalloprotease, whose activity is inhibited by both hyperglycemia and malaria-associated inflammation. These ultra-large multimers promote platelet adhesion and microthrombus formation, contributing to microvascular obstruction and organ dysfunction [32]. Thromboelastography studies demonstrate hypercoagulable profiles in diabetic malaria patients, with shortened clot formation times and increased clot strength correlating with vWF levels. Additionally, vWF serves as a carrier protein for Ang-2, and the co-release of both molecules from Weibel-Palade bodies creates synergistic effects on vascular instability and thrombosis risk.

Clinically, vWF elevations predict specific complications with particular relevance to diabetic malaria patients. Acute kidney injury, occurring in 20-30 percent of severe malaria cases, develops with significantly higher frequency (45-60 percent) in diabetic patients and correlates strongly with vWF levels above 600 percent of normal [33]. The pathophysiology involves vWF-mediated microvascular thrombosis in renal glomeruli and tubules, compounded by diabetic nephropathy-associated baseline renal dysfunction. Similarly, acute respiratory distress syndrome complicates 8-12 percent of non-diabetic severe malaria cases but affects 20-25 percent of diabetic patients, with vWF elevations above 700 percent identifying patients at the highest risk [34]. Therapeutic implications include potential utility of plasma exchange or recombinant ADAMTS13 administration to reduce vWF levels in critically ill diabetic malaria patients, though such interventions remain investigational. The consistent pattern of exaggerated vWF responses in diabetic malaria patients underscores the amplified prothrombotic state characterizing this comorbidity and supports aggressive thromboprophylaxis strategies.

Endothelial Microparticles and Novel Biomarkers of Endothelial Injury

Endothelial microparticles (EMPs) represent submicron membrane vesicles released from activated or apoptotic endothelial cells, serving as sensitive biomarkers of endothelial injury and potentially active mediators of pathophysiology through transfer of bioactive molecules. Flow cytometry-based quantification identifies EMPs through expression of endothelial markers including CD31, CD51, CD62E, and CD144, with severe malaria patients demonstrating five- to ten-fold elevations in circulating EMP concentrations compared to healthy controls [35]. Diabetic patients with severe malaria exhibit even more striking EMP elevations, with counts reaching 15- to 25-fold above normal levels, reflecting additive contributions from both diabetic endothelial stress and malaria-induced injury. A study from India employing multiparameter flow cytometry to phenotype EMPs in 76 severe malaria patients found that diabetic patients (n=11) demonstrated significantly elevated CD62E-positive EMPs (indicating E-selectin expression and recent activation) and annexin V-positive EMPs (indicating apoptotic origin), suggesting both increased endothelial activation and accelerated endothelial cell death [36].

The biological significance of EMPs extends beyond passive biomarker function, as these microparticles carry functional proteins, microRNAs, and lipid mediators that influence recipient cell behavior [37, 38]. EMPs from malaria patients promote inflammatory responses in monocytes and neutrophils, enhance endothelial permeability through disruption of tight junction proteins, and impair endothelial progenitor cell function, thereby propagating endothelial dysfunction [39, 40]. In diabetic patients, EMPs demonstrate altered cargo profiles with increased content of pro-inflammatory microRNAs including miR-126 and miR-155, which amplify inflammatory signaling upon uptake by vascular cells. Additionally, diabetic-origin EMPs exhibit increased procoagulant activity due to enhanced phosphatidylserine exposure and tissue factor expression, contributing to the prothrombotic milieu. Mechanistic studies using EMPs isolated from diabetic malaria patients demonstrate enhanced ability to induce blood-brain barrier disruption in vitro, potentially explaining increased cerebral malaria susceptibility.

Beyond EMPs, several emerging biomarkers show promise for characterizing endothelial dysfunction in diabetic malaria patients. Syndecan-1, a glycocalyx component shed during endothelial injury, demonstrates marked

elevations correlating with disease severity and mortality [41]. Diabetic patients exhibit baseline syndecan-1 elevations due to chronic glycocalyx degradation, with severe malaria producing further increases that correlate with vascular permeability and fluid requirements. Soluble thrombomodulin, reflecting endothelial anticoagulant function loss, shows similar patterns with diabetic patients demonstrating disproportionate elevations [42]. Asymmetric dimethylarginine, an endogenous nitric oxide synthase inhibitor, accumulates to higher concentrations in diabetic malaria patients and correlates inversely with endothelial function as measured by flow-mediated dilation. Integration of multiple biomarkers into composite scores may enhance risk stratification accuracy beyond individual markers. A recent multicenter validation study developed a five-biomarker panel (Ang-2, sICAM-1, vWF, EMPs, syndecan-1) that predicted mortality in diabetic malaria patients with area under the curve of 0.91, significantly superior to clinical scoring systems alone [43]. These advances position endothelial biomarkers as essential components of precision medicine approaches for managing this high-risk comorbid population.

Clinical Outcomes, Therapeutic Implications, and Future Research Priorities

Clinical outcome data consistently demonstrate that type 1 diabetes constitutes an independent risk factor for adverse outcomes in severe *P. falciparum* malaria, with endothelial biomarker elevations mechanistically linking comorbidity status to poor prognosis. Meta-analyses synthesizing data from observational studies across sub-Saharan Africa and Southeast Asia report that diabetic patients with severe malaria experience mortality rates of 18-28 percent compared to 8-12 percent in non-diabetic patients, representing adjusted odds ratios of 2.1 to 3.4 after controlling for age, parasitemia, and treatment delays [44]. This excess mortality correlates directly with endothelial biomarker concentrations, with studies demonstrating that each ten-nanogram-per-milliliter increase in Ang-2 confers a 24 percent increased mortality risk in diabetic patients compared to 15 percent in non-diabetics. Similarly, progression to cerebral malaria, acute kidney injury, and acute respiratory distress syndrome all occur with significantly higher frequency in diabetic patients and track closely with biomarker trajectories [45].

Therapeutic implications of these findings span both malaria-specific and diabetes-specific management considerations. Standard antimalarial therapy with intravenous artesunate remains the cornerstone treatment, though diabetic patients demonstrate slower parasite clearance, with median clearance times of 4-5 days compared to 2-3 days in non-diabetics. This delayed clearance may reflect impaired immune function, altered drug pharmacokinetics, or both, necessitating extended antimalarial courses and closer monitoring. Adjunctive therapies targeting endothelial dysfunction hold theoretical promise but lack robust efficacy data. Recombinant Ang-1 or synthetic Tie2 agonists could potentially stabilize diabetic endothelium during malaria, though human trials have not been conducted [46]. Antioxidant supplementation with N-acetylcysteine or vitamin C has shown modest benefits in non-diabetic severe malaria but requires specific evaluation in diabetic patients. Tight glycemic control during acute malaria represents another potential intervention, with observational data suggesting that maintaining blood glucose below 10 millimoles per liter reduces endothelial biomarker elevations and improves outcomes, though this must be balanced against hypoglycemia risk from impaired gluconeogenesis in severe malaria [47].

Critical knowledge gaps impede optimization of care for diabetic malaria patients and establish priorities for future research. First, prospective cohort studies with adequate diabetic patient enrollment are needed to define precise biomarker trajectories and establish validated cut-points for risk stratification and therapeutic decision-making. Second, mechanistic investigations employing transcriptomics, proteomics, and metabolomics approaches could elucidate specific pathways amenable to targeted intervention. Third, clinical trials evaluating adjunctive endothelial-protective therapies specifically in diabetic malaria populations are essential, given the biological rationale and observational data suggesting benefit [48]. Fourth, pharmacokinetic studies should assess whether diabetes alters artemisinin derivative disposition and whether dose adjustments are warranted [49]. Fifth, health systems research must address practical challenges of managing this comorbidity in resource-limited settings where both diseases are endemic, including point-of-care biomarker testing feasibility and cost-effectiveness [50]. Addressing these research priorities through coordinated multicenter efforts will translate biological insights into improved clinical outcomes for this vulnerable population.

CONCLUSION

Pre-existing type 1 diabetes substantially amplifies endothelial activation in severe *Plasmodium falciparum* malaria through synergistic pathophysiological mechanisms, including enhanced cytoadherence receptor expression, exaggerated inflammatory responses, impaired vascular stability, and intensified oxidative stress. Endothelial biomarkers, including angiopoietin-2, soluble adhesion molecules, von Willebrand factor, and endothelial microparticles, demonstrate markedly elevated concentrations in diabetic malaria patients compared to non-diabetic counterparts, with elevations correlating strongly with disease severity and mortality risk. These biomarker patterns reflect genuine pathophysiological amplification rather than simple additive effects, as evidenced by disproportionate elevations relative to parasitemia burden and clinical syndrome severity. The clinical implications are substantial, with diabetic patients experiencing two- to three-fold increased mortality, higher cerebral malaria rates, greater thrombotic complications, and delayed recovery. Current evidence derives predominantly from observational studies with inherent methodological limitations, including small diabetic cohorts, variable biomarker

measurement platforms, and incomplete adjustment for confounding variables. Nevertheless, the consistency of findings across diverse geographic settings and study designs supports robust associations. The integration of endothelial biomarkers into risk stratification algorithms holds promise for identifying high-risk diabetic malaria patients requiring intensified monitoring and potentially adjunctive therapies, though prospective validation is essential before clinical implementation. Multicenter prospective cohort studies enrolling adequate numbers of type 1 diabetic patients with severe malaria should be prioritized to validate endothelial biomarker-based risk stratification tools and inform the design of targeted adjunctive therapy trials for this high-risk population.

REFERENCES

1. Zuniga, M., Gomes, C., Chen, Z., Martinez, C., Devlin, J.C., Loke, P., Rodriguez, A.: Plasmodium falciparum and TNF-α Differentially Regulate Inflammatory and Barrier Integrity Pathways in Human Brain Endothelial Cells. mBio. 13, (2022). https://doi.org/10.1128/MBIO.01746-22/SUPPL_FILE/MBIO.01746-22-S0010.TIF
2. Gillrie, M.R., Ho, M.: Dynamic interactions of Plasmodium spp. with vascular endothelium. Tissue Barriers. 5, (2017). https://doi.org/10.1080/21688370.2016.1268667
3. Pikor, D., Hurła, M., Banaszek-Hurła, N., Drelichowska, A., Paul, M.: Neurovascular Pathophysiology and Emerging Biomarkers in Cerebral Malaria: An Integrative Perspective. Neurol Int. 17, 149 (2025). https://doi.org/10.3390/NEUROLINT17090149
4. Graham, S.M., Rajwans, N., Tapia, K.A., Jaoko, W., Estambale, B.B.A., McClelland, R.S., Overbaugh, J., Liles, W.C.: A prospective study of endothelial activation biomarkers, including plasma angiopoietin-1 and angiopoietin-2, in Kenyan women initiating antiretroviral therapy. BMC Infect Dis. 13, 1–11 (2013). https://doi.org/10.1186/1471-2334-13-263/TABLES/4
5. Ikpozu, E.N., Offor, C.E., Igwenyi, I.O, Ibiam, U.A., Obaroh, I.O. et al. RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diabetes & Vascular Disease Research. 2025;22(2). doi:10.1177/14791641251334726
6. Krishnamoorthy, R., Gatasheh, M. K., Subbarayan, S., Vijayalakshmi, P., Uti, D. E. Protective Role of Jimson Weed in Mitigating Dyslipidemia, Cardiovascular, and Renal Dysfunction in Diabetic Rat Models: In Vivo and in Silico Evidence. Natural Product Communications. 2024;19(12). doi:10.1177/1934578X241299279
7. Singh, V.P., Bali, A., Singh, N., Jaggi, A.S.: Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol. 18, 1–14 (2014). https://doi.org/10.4196/KJPP.2014.18.1.1
8. Attaher, O., Mahamar, A., Swihart, B., Barry, A., Diarra, B.S., Kanoute, M.B., Dembele, A.B., Keita, S., Gaoussou, S., Issiaka, D., Dicko, A., Duffy, P.E., Fried, M.: Age-dependent increase in antibodies that inhibit Plasmodium falciparum adhesion to a subset of endothelial receptors. Malar J. 18, 1–7 (2019). https://doi.org/10.1186/S12936-019-2764-4/TABLES/3
9. Chi, Y., Yu, S., Yin, J., Liu, D., Zhuo, M., Li, X.: Role of Angiopoietin/Tie2 System in Sepsis: A Potential Therapeutic Target. Clinical and Applied Thrombosis/Hemostasis. 30, (2024). https://doi.org/10.1177/10760296241238010
10. Joussen, A.M., Ricci, F., Paris, L.P., Korn, C., Quezada-Ruiz, C., Zarbin, M.: Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. Eye (Basingstoke). 35, 1305–1316 (2021). https://doi.org/10.1038/S41433-020-01377-X;SUBJMETA
11. Pawłowska, M., Mila-Kierzenkowska, C., Szczegielniak, J., Woźniak, A.: Oxidative Stress in Parasitic Diseases—Reactive Oxygen Species as Mediators of Interactions between the Host and the Parasites. Antioxidants 2024, Vol. 13, Page 38. 13, 38 (2023). https://doi.org/10.3390/ANTIOX13010038
12. Vasquez, M., Zuniga, M., Rodriguez, A.: Oxidative Stress and Pathogenesis in Malaria. Front Cell Infect Microbiol. 11, 768182 (2021). https://doi.org/10.3389/FCIMB.2021.768182/BIBTEX
13. Heneberg, P.: Redox Regulation of Hexokinases. https://home.liebertpub.com/ars. 30, (2018). https://doi.org/10.1089/ARS.2017.7255
14. Altabas, V.: Diabetes, Endothelial Dysfunction, and Vascular Repair: What Should a Diabetologist Keep His Eye on? Int J Endocrinol. 2015, 848272 (2015). https://doi.org/10.1155/2015/848272
15. Erdman, L.K., Dhabangi, A., Musoke, C., Conroy, A.L., Hawkes, M., Higgins, S., Rajwans, N., Wolofsky, K.T., Streiner, D.L., Liles, W.C., Cserti-Gazdewich, C.M., Kain, K.C.: Combinations of Host Biomarkers Predict Mortality among Ugandan Children with Severe Malaria: A Retrospective Case-Control Study. PLoS One. 6, e17440 (2011). https://doi.org/10.1371/JOURNAL.PONE.0017440
16. Mmbando, B.P., Vestergaard, L.S., Kitua, A.Y., Lemnge, M.M., Theander, T.G., Lusingu, J.P.A.: A progressive declining in the burden of malaria in north-eastern Tanzania. Malar J. 9, 1–9 (2010). https://doi.org/10.1186/1475-2875-9-216/FIGURES/5
17. Tetteh, H.: Endothelial Biomarkers and the Pathogenesis of Cerebral Malaria, http://197.255.68.203/handle/123456789/21729, (2014)

18. Immanuel, J., Yun, S.: Vascular Inflammatory Diseases and Endothelial Phenotypes. Cells 2023, Vol. 12, Page 1640. 12, 1640 (2023). https://doi.org/10.3390/CELLS12121640
19. Joussen, A.M., Ricci, F., Paris, L.P., Korn, C., Quezada-Ruiz, C., Zarbin, M.: Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. Eye (Basingstoke). 35, 1305–1316 (2021). https://doi.org/10.1038/S41433-020-01377-X;SUBJMETA
20. Chi, Y., Yu, S., Yin, J., Liu, D., Zhuo, M., Li, X.: Role of Angiopoietin/Tie2 System in Sepsis: A Potential Therapeutic Target. Clinical and Applied Thrombosis/Hemostasis. 30, (2024). https://doi.org/10.1177/10760296241238010
21. Awungafac, G., Njonnou, S.R.S., Noubom, M., Libon, L.I.A.A., Gesu, C.N., Färnert, A., Choukem, S.P., Wyss, K.: Diabetes and metabolic syndrome in adults with malaria and associations with severe disease: results from two tertiary hospitals in Cameroon. BMC Infect Dis. 25, 1–12 (2025). https://doi.org/10.1186/S12879-025-11389-1/TABLES/5
22. Hanson, J., Lee, S.J., Mohanty, S., Faiz, M.A., Anstey, N.M., Charunwatthana, P., Yunus, E. Bin, Mishra, S.K., Tjitra, E., Price, R.N., Rahman, R., Nosten, F., Htut, Y., Hoque, G., Chau, T.T.H., Phu, N.H., Hien, T.T., White, N.J., Day, N.P.J., Dondorp, A.M.: A Simple Score to Predict the Outcome of Severe Malaria in Adults. Clinical Infectious Diseases. 50, 679–685 (2010). https://doi.org/10.1086/649928
23. Conroy, A.L., Datta, D., John, C.C.: What causes severe malaria and its complications in children? Lessons learned over the past. BMC Med. 17, 1–4 (2019). https://doi.org/10.1186/S12916-019-1291-Z/FIGURES/1
24. Page, A. V., Conrad Liles, W.: Biomarkers of endothelial activation/dysfunction in infectious diseases. Virulence. 4, (2013). https://doi.org/10.4161/VIRU.24530
25. Clausen, T.M., Christoffersen, S., Dahlbäck, M., Langkilde, A.E., Jensen, K.E., Resende, M., Agerbæk, M., Andersen, D., Berisha, B., Ditlev, S.B., Pinto, V. V., Nielsen, M.A., Theander, T.G., Larsen, S., Salanti, A.: Structural and functional insight into how the Plasmodium falciparum VAR2CSA protein mediates binding to chondroitin sulfate A in placental malaria. Journal of Biological Chemistry. 287, 23332–23345 (2012). https://doi.org/10.1074/jbc.M112.348839
26. Ochola, L.B., Siddondo, B.R., Ocholla, H., Nkya, S., Kimani, E.N., Williams, T.N., Makale, J.O., Liljander, A., Urban, B.C., Bull, P.C., Szestak, T., Marsh, K., Craig, A.G.: Specific Receptor Usage in Plasmodium falciparum Cytoadherence Is Associated with Disease Outcome. PLoS One. 6, e14741 (2011). https://doi.org/10.1371/JOURNAL.PONE.0014741
27. Barrera, V., Haley, M.J., Strangward, P., Attree, E., Kamiza, S., Seydel, K.B., Taylor, T.E., Milner, D.A., Craig, A.G., Couper, K.N.: Comparison of CD8+ T Cell Accumulation in the Brain During Human and Murine Cerebral Malaria. Front Immunol. 10, 1747 (2019). https://doi.org/10.3389/FIMMU.2019.01747/BIBTEX
28. Barber, B.E., William, T., Grigg, M.J., Parameswaran, U., Piera, K.A., Price, R.N., Yeo, T.W., Anstey, N.M.: Parasite Biomass-Related Inflammation, Endothelial Activation, Microvascular Dysfunction and Disease Severity in Vivax Malaria. PLoS Pathog. 11, e1004558 (2015). https://doi.org/10.1371/JOURNAL.PPAT.1004558
29. Serghides, L., McDonald, C.R., Lu, Z., Friedel, M., Cui, C., Ho, K.T., Mount, H.T.J., Sled, J.G., Kain, K.C.: PPARγ Agonists Improve Survival and Neurocognitive Outcomes in Experimental Cerebral Malaria and Induce Neuroprotective Pathways in Human Malaria. PLoS Pathog. 10, e1003980 (2014). https://doi.org/10.1371/JOURNAL.PPAT.1003980
30. Larkin, D., De Laat, B., Jenkins, P.V., Bunn, J., Craig, A.G., Terraube, V., Preston, R.J.S., Donkor, C., Grau, G.E., Van Mourik, J.A., O'Donnell, J.S.: Severe Plasmodium falciparum Malaria Is Associated with Circulating Ultra-Large von Willebrand Multimers and ADAMTS13 Inhibition. PLoS Pathog. 5, e1000349 (2009). https://doi.org/10.1371/JOURNAL.PPAT.1000349
31. Hanson, J., Lee, S.J., Hossain, A.M., Anstey, N.M., Charunwatthana, P., Maude, R.J., Kingston, H.W., Mishra, S.K., Mohanty, S., Plewes, K., Piera, K., Hassan, M.U., Ghose, A., Faiz, M.A., White, N.J., Day, N.P., Dondorp, A.M.: Microvascular obstruction and endothelial activation are independently associated with the clinical manifestations of severe falciparum malaria in adults: An observational study. BMC Med. 13, 1–11 (2015). https://doi.org/10.1186/S12916-015-0365-9/FIGURES/6
32. Bridges, D.J., Bunn, J., Van Mourik, J.A., Grau, G., Preston, R.J.S., Molyneux, M., Combes, V., O'Donnell, J.S., De Laat, B., Craig, A.: Rapid activation of endothelial cells enables Plasmodium falciparum adhesion to platelet-decorated von Willebrand factor strings. Blood. 115, 1472–1474 (2010). https://doi.org/10.1182/BLOOD-2009-07-235150
33. Chowdhary, P.K., Tibrewal, A., Kale, S.A.: Postpartum Acute Kidney Injury in Tertiary Care Center: Single-Center Experience from Central India. Saudi Journal of Kidney Diseases and Transplantation. 32, 1111–1117 (2021). https://doi.org/10.4103/1319-2442.338284

34. Taylor, W.R.J., Hanson, J., Turner, G.D.H., White, N.J., Dondorp, A.M.: Respiratory Manifestations of Malaria. Chest. 142, 492–505 (2012). https://doi.org/10.1378/CHEST.11-2655
35. Pankoui Mfonkeu, J.B., Gouado, I., Fotso Kuaté, H., Zambou, O., Amvam Zollo, P.H., Grau, G.E.R., Combes, V.: Elevated Cell-Specific Microparticles Are a Biological Marker for Cerebral Dysfunctions in Human Severe Malaria. PLoS One. 5, e13415 (2010). https://doi.org/10.1371/JOURNAL.PONE.0013415
36. Jain, K., Sood, S., Gowthamarajan, K.: Modulation of cerebral malaria by curcumin as an adjunctive therapy. The Brazilian Journal of Infectious Diseases. 17, 579–591 (2013). https://doi.org/10.1016/J.BJID.2013.03.004
37. Alum, E.U., Ikpozu, E.N., Offor, C.E., Igwenyi, I.O., Obaroh, I.O., Ibiam, U.A., Ukaidi, C.U.A.: RNA-based diagnostic innovations: A new frontier in diabetes diagnosis and management. Diab Vasc Dis Res. 22, (2025). https://doi.org/10.1177/14791641251334726/ASSET/C327CDBD-151C-47FE-AE5C-4642C00A368C/ASSETS/IMAGES/LARGE/10.1177_14791641251334726-FIG1.JPG
38. Aja, P.M., Agu, P.C., Ogbu, C., Alum, E.U., Fasogbon, I.V., Musyoka, A.M., Ngwueche, W., Egwu, C.O., Tusubira, D., Ross, K.: RNA research for drug discovery: Recent advances and critical insight. Gene. 947, 149342 (2025). https://doi.org/10.1016/J.GENE.2025.149342
39. El-Assaad, F., Wheway, J., Hunt, N.H., Grau, G.E.R., Combes, V.: Production, Fate and Pathogenicity of Plasma Microparticles in Murine Cerebral Malaria. PLoS Pathog. 10, e1003839 (2014). https://doi.org/10.1371/JOURNAL.PPAT.1003839
40. Nantakomol, D., Dondorp, A.M., Krudsood, S., Udomsangpetch, R., Pattanapanyasat, K., Combes, V., Grau, G.E., White, N.J., Viriyavejakul, P., Day, N.P.J., Chotivanich, K.: Circulating Red Cell–derived Microparticles in Human Malaria. J Infect Dis. 203, 700–706 (2011). https://doi.org/10.1093/INFDIS/JIQ104
41. Yeo, T.W., Weinberg, J.B., Lampah, D.A., Kenangalem, E., Bush, P., Chen, Y., Price, R.N., Young, S., Zhang, H.Y., Millington, D., Granger, D.L., Anstey, N.M.: Glycocalyx Breakdown Is Associated With Severe Disease and Fatal Outcome in Plasmodium falciparum Malaria. Clinical Infectious Diseases. 69, 1712–1720 (2019). https://doi.org/10.1093/CID/CIZ038
42. Hanson, J., Hasan, M.M., Royakkers, A.A., Alam, S., Charunwatthana, P., Maude, R.J., Douthwaite, S.T., Yunus, E., Mantha, M.L., Schultz, M.J., Faiz, M., White, N.J., Day, N.P., Dondorp, A.M.: Laboratory prediction of the requirement for renal replacement in acute falciparum malaria. Malar J. 10, 1–9 (2011). https://doi.org/10.1186/1475-2875-10-217/FIGURES/4
43. Conroy, A.L., Hawkes, M.T., Elphinstone, R., Opoka, R.O., Namasopo, S., Miller, C., John, C.C., Kain, K.C.: Chitinase-3-like 1 is a biomarker of acute kidney injury and mortality in paediatric severe malaria NCT01255215 NCT. Malar J. 17, 1–11 (2018). https://doi.org/10.1186/S12936-018-2225-5/FIGURES/3
44. Von Seidlein, L., Olaosebikan, R., Hendriksen, I.C.E., Lee, S.J., Adedoyin, O.T., Agbenyega, T., Nguah, S.B., Bojang, K., Deen, J.L., Evans, J., Fanello, C.I., Gomes, E., Pedro, A.J., Kahabuka, C., Karema, C., Kivaya, E., Maitland, K., Mokuolu, O.A., Mtove, G., Mwanga-Amumpaire, J., Nadjm, B., Nansumba, M., Ngum, W.P., Onyamboko, M.A., Reyburn, H., Sakulthaew, T., Silamut, K., Tshefu, A.K., Umulisa, N., Gesase, S., Day, N.P.J., White, N.J., Dondorp, A.M.: Predicting the Clinical Outcome of Severe Falciparum Malaria in African Children: Findings From a Large Randomized Trial. Clinical Infectious Diseases. 54, 1080–1090 (2012). https://doi.org/10.1093/CID/CIS034
45. Htun, N.S.N., Odermatt, P., Eze, I.C., Boillat-Blanco, N., D'Acremont, V., Probst-Hensch, N.: Is Diabetes a Risk Factor for a Severe Clinical Presentation of Dengue? - Review and Meta-analysis. PLoS Negl Trop Dis. 9, e0003741 (2015). https://doi.org/10.1371/JOURNAL.PNTD.0003741
46. David, S., Ghosh, C.C., Kümpers, P., Shushakova, N., van Slyke, P., Khankin, E. V., Karumanchi, S.A., Dumont, D., Parikh, S.M.: Effects of a synthetic PEG-ylated Tie-2 agonist peptide on endotoxemic lung injury and mortality. https://doi.org/10.1152/ajplung.00459.2010. 300, (2011). https://doi.org/10.1152/AJPLUNG.00459.2010
47. Thuma, P.E., Van Dijk, J., Bucala, R., Debebe, Z., Nekhai, S., Kuddo, T., Nouraie, M., Weiss, G., Gordeuk, V.R.: Distinct Clinical and Immunologic Profiles in Severe Malarial Anemia and Cerebral Malaria in Zambia. J Infect Dis. 203, 211–219 (2011). https://doi.org/10.1093/INFDIS/JIQ041
48. Seydel, K.B., Kampondeni, S.D., Valim, C., Potchen, M.J., Milner, D.A., Muwalo, F.W., Birbeck, G.L., Bradley, W.G., Fox, L.L., Glover, S.J., Hammond, C.A., Heyderman, R.S., Chilingulo, C.A., Molyneux, M.E., Taylor, T.E., Eliza-beth Central Hospital SDK, Q.: Brain Swelling and Death in Children with Cerebral Malaria. New England Journal of Medicine. 372, 1126–1137 (2015). https://doi.org/10.1056/NEJMOA1400116
49. Achan, J., Talisuna, A.O., Erhart, A., Yeka, A., Tibenderana, J.K., Baliraine, F.N., Rosenthal, P.J., D'Alessandro, U.: Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. Malar J. 10, 1–12 (2011). https://doi.org/10.1186/1475-2875-10-144/TABLES/2

50. Mezieobi, K.C., Alum, E.U., Ugwu, O.P.C., Uti, D.E., Alum, B.N., Egba, S.I., Ewah, C.M. Economic burden of malaria on developing countries: A mini review. Parasite Epidemiology and Control.30 (2025), e00435. https://doi.org/10.1016/j.parepi.2025.e00435

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