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ORIGINAL RESEARCH

An Assessment of Endothelial Markers in Patients with Uncomplicated Malaria in Jazan Province, Saudi Arabia

Aymen Madkhali[1], Gasim Dobie[1], Abdullah A Mobarki[1], Khaled Essawi[1], Waleed Hakami[1], Abdulrahim R Hakami[2], Mohammed H Nahari[3], Yahya H Matari[4], Raneem Alhazmi[5], Mohammed Alkurbi[6], Shaqraa Musawi[1], Yara Alyahyawi[1], Fatemah A Alhakami[1], Mohammad S Akhter[1,7], Muhammad Saboor[8,9], Ali Hakamy[10], Hassan A Hamali[1]

[1]Department of Medical Laboratory Technology, College of Nursing and Health Sciences, Jazan University, Jazan, Saudi Arabia; [2]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, Abha, Saudi Arabia; [3]Department of Medical Laboratory Technology, Najran University, Najran, Saudi Arabia; [4]Department of Hematology and Blood Bank, Baish General Hospital, Jazan, Saudi Arabia; [5]Riyadh Medical Clinic Complex, Riyadh, Saudi Arabia; [6]Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia; [7]Health Research Center, Jazan University, Jazan, Saudi Arabia; [8]Department of Medical Laboratory Sciences, College of Health Sciences, University of Sharjah, Sharjah, United Arab Emirates; [9]Research Institute for Medical and Health Sciences, University of Sharjah, Sharjah, United Arab Emirates; [10]Nursing Department, College of Nursing and Health Sciences, Jazan University, Jazan, Saudi Arabia

Correspondence: Hassan A Hamali; Aymen Madkhali, Department of Medical Laboratory Technology, College of Nursing and Health Sciences, Jazan University, P.O. Box 1906, Gizan, 45142, Saudi Arabia, Email hhamali@jazanu.edu.sa; ammadkhali@jazanu.edu.sa

Background: Malaria continues to be a life-threatening disease that affects people in tropical and sub-tropical regions. Endothelial cells play a key role in the pathogenicity and severity of malaria. This study aimed to assess circulating endothelial cell markers and their correlation with routine laboratory parameters and parasite density in malaria patients compared to matched healthy controls.

Materials and Methods: This study included 34 patients with non-severe *P. falciparum* malaria and 34 matched-healthy controls from the Jazan region. Plasma levels of circulating endothelial markers, including (E-selectin, intercellular adhesion molecule-1 [ICAM-1], and vascular cell adhesion molecule-1 [VCAM-1]) were measured in the study cohort.

Results: The findings revealed significantly elevated levels of E-selectin, ICAM-1, and VCAM-1 in malaria patients compared to controls. In addition, multivariable analysis indicated that age, hemoglobin levels, platelet counts, prothrombin time, and E-selectin levels were significantly associated with malaria infection, but no association was found between circulating endothelial markers and parasite density.

Conclusion: The data suggest a significant role for E-selectin, ICAM-1, and VCAM-1 in the pathogenesis of malaria infection and their potential use alongside laboratory parameters as indicators of endothelial dysfunction in malaria.

Keywords: malaria, endothelial cell markers, E-selectin, ICAM-1, VCAM-1, laboratory parameters

Introduction

Malaria remains a life-threatening disease and a significant global public health burden, particularly in tropical and subtropical regions.[1] Despite extensive global efforts to eradicate malaria and improve health outcomes, particularly in regions with endemic transmission, the disease remains a persistent challenge to healthcare and community due to its transmission dynamics, drug resistance, and resilience control measures.[1] Prompt and accurate diagnosis of malaria is crucial for its effective management. Early identification of complications helps reduce the associated health risks. Significant advances have been made in understanding malaria pathogenesis; however, substantial efforts are still needed to develop novel treatment options and improve treatment outcomes. These include the development of more effective antimalarial drugs and vaccines, along with integrated vector management approaches to control the spread of the disease.[2,3]

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The pathogenesis of malaria is complex and involves multiple stages throughout the course of the infection. A key factor is sequestration, where infected erythrocytes (IEs) adhere to endothelial cells lining the microvasculature.[4–6] Cyto-adhesion (mediated by endothelial markers) plays a pivotal role in the sequestration process of *Plasmodium (P) falciparum* IEs, a key mechanism in the pathogenesis of severe malaria. This process is mediated by intricate interactions between the *P. falciparum*-IEs and a wide range of human endothelial cell receptors.[4–6]

Malaria outcomes depend on the type of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) expression and the specific endothelial receptors involved in cyto-adhesion. This interaction is a key factor in the pathogenesis of malaria, leading to adhesion of IEs to the endothelial lining of blood vessels.[6] The diversity and specificity of these interactions are primarily dictated by the variable expression of PfEMP1 on the surface of IEs.[6] Malaria pathogenesis is largely influenced by the interaction of PfEMP-1 with endothelial receptors such as Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), and E-selectin. These interactions are critical for the cytoadherence of IEs to endothelial cells and lead to parasite sequestration and vascular blockage. Studies have shown that these endothelial markers are elevated during malaria infection, but their precise role in febrile, uncomplicated, and severe malaria remains to be fully understood.[7]

Given the limited research on the effects of malaria infection and its interaction with endothelial cells in the Jazan region of Saudi Arabia, this study aimed to (i) assess the levels of endothelial markers (adhesion molecules including ICAM-1, VCAM-1, and E-selectin) in malaria patients and (ii) correlate these levels with hematological parameters and parasite density. This research endeavor is vital for advancing our understanding of malaria pathogenesis in this specific region, and for developing more effective region-specific treatment strategies.

Materials and Methods

Study Design

This current study is a case control involving 34 patients with non-severe *P. falciparum* malaria infection and 34 matched healthy controls from the Jazan region, Saudi Arabia. *P. falciparum* malaria infections were diagnosed using thin and thick blood smears and rapid diagnostic tests (RDT) as previously described.[8] The control group consisted of healthy blood donors with no history of fever, symptoms, or chronic diseases. Additionally, these healthy blood donors tested negative for malaria, sickle cell, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and syphilis.

Whole blood was collected from the patients and controls into ethylenediaminetetraacetic acid (EDTA) for complete blood count (CBC) analysis and sodium citrate tubes to assess the levels of circulating, soluble endothelial markers, including E-selectin, ICAM-1, and VCAM-1. CBC parameters were obtained using a Sysmex XN-550 hematology Analyzer (Sysmex, Kobe, Japan). Giemsa-stained thin and thick blood films were prepared to confirm malaria infection and evaluate parasitemia. Parasite density was estimated and categorized into four groups low, mild, moderate, and high.[9]

Plasma was obtained from sodium citrate tubes by centrifuging blood at 3000 rpm for 30 min at room temperature. Plasma was carefully removed and divided into two aliquots; one aliquot was used for coagulation profile analysis, while the other aliquot was stored at −80°C for the analysis of circulating endothelial cell makers. The coagulation profile including prothrombin time (PT) and activated partial thromboplastin time (aPTT) was evaluated in plasma using a stage compact analyzer (Diagnostica Stago, France). The circulating endothelial cell markers E-selectin, ICAM, and VCAM were measured in plasma using ELISA kits from MyBioSource (CA, USA).

Ethical Consideration

This study was approved by the Jazan Research Ethics Committee (Ref. No. 086) and carried out according to the Declaration of Helsinki. Informed consent was obtained from all adult participants and from the children's guardians.

Statistical Analysis

GraphPad Prism (version 8.0) was used for statistical analysis. The data in the study were analyzed using the chi-square test for demographic data. The unpaired *t*-test was applied to normally distributed data, and the Man-Whitney was applied to data that were not normally distributed. Correlation studies were analyzed using a single-sample *t*-test. Additionally, multivariate linear regression analysis was used to determine the association of independent variables with malaria infection. Data are presented as mean ± standard deviation. A p-value of less than <0.05 was considered significant.

Results

Demographic Characteristics and Hematological Parameters

A total of 68 participants, including *P. falciparum*-infected malaria patients and healthy matched controls, were recruited for the current study and their demographic characteristics, hematological and coagulation parameters are illustrated in (Table 1). The malaria-infected group consisted of 28 males and 6 females, while the healthy controls comprised 24 males and 10 females. The CBC data of patients with malaria infection differed significantly from the matched healthy controls ($p<0.05$; Table 1). In the patient group, red blood cell (RBC) count, hemoglobin, and platelet count were significantly lower compared to the controls ($p<0.05$; Table 1), while white blood cell (WBC) count was slightly increased but without any statistical significance ($p>0.05$; Table 1). Malaria patients had significantly lower PT and aPTT than the controls ($p<0.05$; Table 1).

Circulating Endothelial Markers

The circulating endothelial markers E-selectin, ICAM-1, and VCAM-1 were significantly elevated in malaria patients compared with controls ($p<0.05$; Table 2). E-selectin was 3.0 ± 0.3 ng/mL in patients compared to 1.0± 0.1 ng/mL in controls ($p<0.0001$). ICAM-1 levels were 3.4 ± 0.2 ng/mL in patients compared to 1.0± 0.2 ng/mL in controls ($p<0.0001$). Lastly, VCAM-1 levels were 0.3 ± 0.5 ng/mL in patients compared to 0.1± 0.2 ng/mL in controls ($p<0.0453$).

Table 1 Demographic, Hematological and Coagulation Parameters for Malaria Patients and Controls.

Parameter	Patients (n=34)	Controls (n=34)	*P* value
Male/female	28/6	24/10	
Age	28.3±15.7	29.0±15.8	>0.5
WBCs (10^9/L)	6.2±1.6	5.6±1.3	0.1161
RBCs (10^{12}/L)	4.7±1.0	5.2±0.4	0.0091
Hb (g/dl)	11.7±2.4	14.1±1.2	<0.0001
Platelets (10^9/L)	114±96	320±62	<0.0001
PT (seconds)	11.9±0.8	14.4±0.9	<0.0001
aPTT (seconds)	29.0±2.3	33.7±1.9	<0.0001

Table 2 Levels of Circulating Endothelial Markers in Malaria Patients and Controls.

Parameter	Patients (n=34)	Controls (n=34)	*P* value
	Mean±SD	Mean±SD	
E selectin (ng/mL)	3.0±0.3	1.0±0.1	<0.0001
ICAM-1 (ng/mL)	3.4±0.2	1.0±0.2	<0.0001
VCAM-1 (ng/mL)	0.3±0.5	0.1±0.2	0.0453

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Correlation Studies of Circulating Endothelial Markers with Hematological and Coagulation Parameters

The study revealed significant correlations between endothelial markers and hematological parameters. A robust correlation was observed between E-selectin and ICAM-1, as well as between ICAM-1 and VCAM-1 (Table 3). E-selectin exhibited a significant negative correlation with key hematological and coagulation parameters, including platelet counts, RBC count, hemoglobin, PT, and aPTT. Conversely, E-selectin had a significant positive correlation with WBC count. ICAM-1 displayed a similar correlation pattern to E-selectin, with negative correlations with the same hematological parameters and a positive correlation with WBC count (Table 3). VCAM-1 also followed this trend, showing similar correlations with hematological parameters and coagulation profiles, including a significant negative correlation with aPTT ($p<0.05$, Table 3).

Multivariate Linear Regression of the Studied Parameters

Multivariable analysis showed that age, hemoglobin, platelets, PT, and E-selectin were significantly associated with malaria infection (Table 4): age (β=0.0.003534, $p<0.01$), hemoglobin (β=−0.03687, $p=0.01$), platelets (β=−0.0007829, $p<0.0001$), PT (β=−0.09484, $p<0.0001$), and E-selectin (β=0.1395, $p<0.05$).

Classification of the CBC and EC Markers Based on Parasitemia Induced by Plasmodium Falciparum

The patient group was subcategorized into four categories based on parasitemia levels. Low parasitemia group with parasite number between 100–1,000/μL, mild parasitemia group with parasite number between 1000–10,000/μL, moderate parasitemia group with parasite number between 10,000–100,000/μL, and high parasitemia group with parasite number >100,000/μL. Our study had fifteen patients with low parasitemia, seven patients with mild parasitemia, twelve patients with moderate parasitemia and none of the patients had high parasitemia in the current study (Table 5). The data showed either no or only minor change with parasitemia, except that the hemoglobin was statistically significant ($p<0.05$).

Table 3 Correlation Between Circulating Endothelial Markers, Hematological Parameters and Coagulation Parameters in the Studied Population.

Parameter	r	R Squared	*P* value
E selectin and ICAM-1	0.9628	0.9269	<0.0001
E selectin and VCAM-1	0.2038	0.04154	0.1062
VCAM-1 and ICAM-1	0.2553	0.06518	0.0418
E selectin and platelets	−0.6900	0.4761	<0.0001
E selectin and RBCs	−0.2808	0.07885	0.0246
E selectin and Hb	−0.4677	0.2188	<0.0001
E selectin and WBCs	0.2629	0.06909	0.0359
E selectin and PT	−0.7193	0.5174	<0.0001
E selectin and aPTT	−0.7594	0.5767	<0.0001
ICAM-1 and platelets	−0.6883	0.4737	<0.0001
ICAM-1 and RBCs	−0.3498	0.1223	0.0046
ICAM-1 and Hb	−0.5136	0.2638	<0.0001
ICAM-1 and WBCs	0.2168	0.04701	0.0853
ICAM-1 and PT	−0.7303	0.5333	<0.0001
ICAM-1 and aPTT	−0.7605	0.5784	<0.0001
VCAM-1 and platelets	−0.2043	0.04175	0.1053
VCAM-1 and RBCs	−0.07195	0.005177	0.5721
VCAM-1 and Hb	−0.2418	0.05847	0.0542
VCAM-1 and WBCs	0.03022	0.0009132	0.8126
VCAM-1 and PT	−0.1494	0.02231	0.2426
VCAM-1 and aPTT	−0.2620	0.06864	0.0381

Table 4 Multivariate Linear Regression of the Study Parameters with Controls and Patients with Malaria.

Variables	Multivariate β Coefficients (95% CI)	*P* value
Age	0.0.003534 (0.0009203 to 0.006148)	0.0090
WBC	0.01453 (−0.01033 to 0.03938)	0.2462
RBCs	0.02655 (−0.03448 to 0.08759)	0.3867
Hemoglobin	−0.03687 (−0.06232 to −0.01143)	0.0053
Platelets	−0.0007829 (−0.001146 to −0.0004197)	<0.0001
PT	−0.09484 (−0.1309 to −0.05880)	<0.0001
aPTT	−0.004781 (−0.02168 to 0.01212)	0.5727
E-selectin	0.1395 (0.01239 to 0.2665)	0.0321
ICAM-1	0.08077 (−0.03153 to 0.1931)	0.1549
VCAM-1	−0.02577 (−0.1187 to 0.06711)	0.5801

Table 5 Sub-Analysis of Levels of Circulating Endothelial Markers and Hematological Parameters According to the Level of Parasitemia in P. Falciparum Malaria Infection.

Parameter	Parasitemia			*P* value
	Low (n=15)	Mild (n=7)	Moderate (n=12)	
Age	22.3±13.5	36.6±12.4	30.8±18.1	0.1090
Male/Female	8/7	5/2	11/1	NA
E-selectin	3.0±0.3	3.1±0.2	3.1±0.3	0.1118
ICAM-1	3.4±0.2	3.4±0.2	3.3±0.2	0.2001
VCAM-1	0.4±0.7	0.2±0.0	0.2±0.00	0.5509
Platelets (10^9/L)	103±76	106±58	133±134	0.7224
RBCs (10^{12}/L)	4.5±0.8	5.0±0.5	4.8±1.4	0.6275
Hb (g/dl)	10.6±2.0	13.9±0.5	11.7±2.8	0.0116
WBCs (10^9/L)	5.9±1.2	6.1±1.6	6.5±2.1	0.6999
PT (seconds)	11.9±0.9	11.8±0.6	12.0±0.7	0.8685
aPTT (seconds)	28.3±1.9	28.4±1.4	27.4±3.2	0.5768

Discussion

E-selectin, ICAM-1, and VCAM-1 serve as key receptors for ligands such as PfEMP1, which are expressed on the surface of IEs and mediate cytoadherence.[10–18] This interaction suggests that reducing the levels of these host molecules could help disrupt pathogen–host interaction.[19] The current study reported elevated levels of circulating endothelial markers including ICAM-1, E-selectin, and VCAM-1 in patients with malaria. These finding are similar to previous reports of non-complicated and complicated malaria infection.[20–22] Furthermore, elevated levels (up to ninefold) of these endothelial marker have been reported in severe cerebral *P. falciparum* malaria.[20]

Frimpong et al, (2021) reported markedly elevated levels of ICAM-1, VEGF-A, and VEGFR2 in children with asymptomatic parasitemia compared to uninfected controls.[23] The role of ICAM-1 in cytoadherence, demonstrated by in vitro binding assays and field studies, remains a subject of scientific discourse, particularly concerning its relationship with *P. falciparum* disease severity. While some studies have suggested a link between elevated ICAM-1 expression and severe *P. falciparum* malaria, particularly in pediatric infections,[17] other findings, such as those of a Malawian study, indicate a negative correlation with disease severity in pediatric cases.[24] In the current study, the significant association between endothelail cell markers (ICAM-1, VCAM-1 and E-selectin) and malaria infection was noted, contributing to the ongoing debate regarding their precise role in disease pathogenesis. In contrast, the more restricted expression profile of E-selectin, and VCAM-1 highlighted a different aspect of the disease's molecular landscape.[20]

Our analysis revealed interesting correlations between adhesion molecules. There was a positive correlation between E-selectin and ICAM-1, and between ICAM-1, and VCAM-1. This suggests that an interconnected network influence

their roles in the pathogenesis of malaria. However, the lack of a statistically significant correlation between E-selectin and VCAM-1 suggests that they may have independent functions in disease progression. Additionally, our study confirmed the characteristic hematological changes seen in malaria, with significantly lower RBC, hemoglobin, and platelet counts in patients compared than in healthy controls. These findings are in agreement with other studies.[25,26] Decreased blood counts are attributed to hemolysis, along with bone marrow dyserythropoiesis. Additionally, malaria-induced thrombocytopenia further complicates the impact of the disease on hematological health.[27] Furthermore, splenic sequestration also contributes to the development of low blood counts.

Conflicting results exist in the literature regarding PT and aPTT in patients with malaria. In our study, PT and aPTT were significantly lower in malaria patients than in controls, although they remained within the normal range in both groups. Similarly, previous studies have reported PT and aPTT to be within normal limits in non-complicated malaria and also in severe *P. falciparum* infections.[28] However, some other findings contrast ours, showing prolonged PT and aPTT in patients with malaria.[29] For instance, prolonged PT and aPTT have been reported in pregnant women with malaria.[30] In malaria patients co-infected with HIV, PT was slightly affected, whereas no effect was observed on aPTT.[31] Prasad et al (2009) also found prolonged PT in 47.5% and prolonged aPTT in 35% of severe malaria cases.[32] Notably, the mean aPTT in our study was 29 seconds, closely matching the 30-second mean reported by Prasad et al (2009).[32]

Correlation analysis revealed a significant negative correlation between PT and E-selectin, ICAM-1, and VCAM-1 levels. Additionally, aPTT negatively correlated with E-selectin ($p<0.05$), ICAM-1 ($p<0.05$), and VCAM-1 ($p>0.05$). The negative correlations between adhesion molecules and various hematological and coagulation parameters, except for a positive correlation with WBC counts, suggest that malaria infection is characterized by a state of endothelial inflammation. This inflammation is intricately linked to a leukocyte-mediated host defense response, highlighting the complex interplay between the pathogen, host immune responses, and vascular dysfunction.

The findings of this study showed no statistically significant differences in the levels of E-selectin, ICAM-1, and VCAM-1 across the subclinical groups with low, mild, and moderate parasitemia (Table 5). This lack of variation may be attributed to the relatively similar inflammatory responses observed in subclinical malaria, where the immune system can mount a response without significant endothelial activation. Subclinical malaria infections often exhibit lower levels of systemic inflammation than severe cases, as the parasite burden is insufficient to trigger widespread endothelial activation and significant cytoadherence-related complications. This may explain the absence of marked differences in adhesion molecule expression, as endothelial dysfunction and vascular changes commonly associated with severe malaria are less pronounced in lower parasitemia levels. Furthermore, subclinical cases often reflect a balance between parasite replication and immune control, limiting the need for a heightened expression of adhesion molecules.

The current study, however, has certain limitations. First, the relatively small sample size may have influenced study outcomes. Additionally, the comorbidities of the patients were not reported, which could have potentially influenced certain hematological and coagulation parameters. Despite these limitations, to the best of our knowledge, they do not detract from the validity of our observation regarding elevated levels of adhesion molecules in malaria.

Our study, conducted in Jazan region of Saudi Arabia, demonstrated a significant increase in circulating endothelial adhesion molecules in patients with malaria. This finding aligns with global research and underscores the consistency of these molecular patterns across diverse geographic regions. The elevated levels of these adhesion molecules not only reflect worldwide trends but also reinforce their potential candidacy as potential therapeutic targets. This is particularly crucial, given the increasing challenges of antimalarial drug resistance and the ineffectiveness of existing combination therapies. Our research adds to the growing body of knowledge on malaria pathogenesis, highlighting the importance of investigating the role of adhesion molecules as potential therapeutic interventions.[33,34] The variability in their expression and effects across different populations highlights the need for tailored, region-specific treatment strategies. Such approaches are essential for addressing the unique challenges faced by regions such as Jazan, which are at the forefront of the battle against malaria.

Conclusions

This study demonstrates significant hematological and coagulation differences in malaria patients as compared to control, characterized by reduced RBCs, hemoglobin, and platelets, as well as shortened PT and aPTT. Elevated E-selectin, ICAM-1, and VCAM-1 levels confirm endothelial activation, with strong inverse correlations between E-selectin/ICAM-

1 and hematological/coagulation markers, while VCAM-1 showed weaker associations. Sub-analysis revealed no significant differences in adhesion molecule levels across parasitemia severities which suggests that endothelial dysfunction occurs independently of parasite burden. These findings emphasize the central role of endothelial activation in malaria pathogenesis and highlight adhesion molecules as potential biomarkers or therapeutic targets.

Abbreviations

ICAM-1, intercellular adhesion molecule; VCAM-1, 1 vascular cell adhesion molecule-1; IE, infected erythrocytes; P, plasmodium; PfEMP1, *P. falciparum* erythrocyte membrane protein 1; EDTA, ethylenediaminetetraacetic acid; CBC, complete blood count; PT, prothrombin time; aPTT, activated partial thromboplastin time; RBC, red blood cell; WBC, while white blood cell.

Data Sharing Statement

The data supporting the findings of this study are available from the authors Hassan A Hamali, Aymen Madkhali and Gasim Dobie upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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