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RESEARCH ARTICLE

Use of Some Surrogate Markers of Inflammation as Predictor of Malaria Severity

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ABSTRACT

Objectives: The role of some basic immune-inflammatory markers in malaria is yet to be investigated in our locality. This study was conducted to determine the relationship between some predictive immune-inflammatory markers and malaria among malaria-infected persons in Benin City, Nigeria.

Methods: EDTA blood specimens were collected from 400 malaria patients attending outpatient clinics and in the wards of major hospitals in Benin City. The blood samples were used for malaria parasite density determination and complete blood count analysis of some basic inflammatory markers such as Neutrophil/Lymphocyte Ratio (NLR), Monocyte/Neutrophil Ratio (MNR), Platelet/Lymphocyte Ratio (PLR), Monocyte/Lymphocyte Ratio (MLR) and Systemic Immune-inflammatory Index (SII) were calculated from the obtained parameter of the Full Blood Count and the data analyzed.

Results: Levels of parasitemia amongst malaria patients were not significantly affected by all the demographic characteristics profiled in this study. Eosinophils percentage count was significantly higher in individuals with high parasitemia (p=0.0121). Of all the Socio-demographic factors analyzed in this study, only living arrangements affected the MPV of malaria patients, showing that MPV was significantly higher in patients living in one room (p=0.0407). Immune inflammatory markers correlated significantly and positively with malaria MLR (r=0.322, p<0.0001), MNR (r=0.241, p<0.0001), NLR (r=0.122, p=0.015), SII (r=0.115, p=0.022) and PLR (r=0.109, p=0.030).

Conclusion: NLR, MNR, MLR, PLR, and SII are positively associated with malaria parasitemia. Therefore, these inflammatory immune markers can be used as a cost-effective way of assessing malaria severity as well as for malaria prognosis. *J Microbiol Infect Dis 2021; 11(4):201-208.*

Keywords: *Immune inflammatory markers, Malaria, Parasitemia, Prognosis*

INTRODUCTION

Malaria is a highly inflammatory disease caused by *Plasmodium spp* transmitted through the bite of female Anopheles mosquitoes to people. It is a preventable and treatable condition that has remained the most important parasitic disease globally [1]. In 2019, it was reported that nearly half of the world's population (3.8 billion people) were at risk of malaria, with it being endemic in 91 countries [2]. There has been recorded significant progress in a reduction in the global malaria burden due to aggressive malaria control and elimination efforts since 2000, resulting in a global reduction of 41% in morbidity and 62% in mortality. Nevertheless, the World Health Organization estimates that there were still 229 million cases in 2019, with 409,000 deaths owing to this disease, 94% of which occurred in Africa [2]. The global

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reduction in morbidity and mortality of malaria had been achieved through active National Malaria Control Programs that emphasize the use of antimalarial therapy, with artemisinin combination therapy being the first-line drug in most countries, including Nigeria [2,3].

Malaria is known to cause a broad range of clinical conditions with several life-threatening organ pathologies up to the cringing cerebral malaria [4]. Like most infectious diseases, malaria initiates inflammatory responses. The eventual outcome of infection depends on the control of immune responses that efficiently clear the parasites and aid the development of protective immunity [5]. In response to parasites, immune responses initiated by the innate immune system play vital roles in protective immunity development and pathogenesis. However, dysregulated host inflammatory responses and endothelial activation play central roles in severe malaria pathogenesis; hence the utility of these host biomarkers of inflammation may extend beyond the prognosis of severe malaria. The white blood cell (WBC) count and its subtypes are classic indicators of inflammation [6]. Also, changes in total and differential leukocyte count during *P. falciparum* infection have been previously described in clinical studies and controlled human malaria infection studies [7,8]. Complete blood counts and differential cell analysis from peripheral blood are used routinely to diagnose many infectious diseases, including malaria. Nevertheless, using these methods as markers of disease risk and inflammation studies seems to have been poorly investigated in our area [9,10].

The platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) have been identified as potential markers of inflammation in various conditions such as tumors and cardiovascular conditions [1-13]. However, there is no study in our locality on the relationship between malaria and these inflammatory markers. Although we have earlier reported the presence of antibodies to artemisinin in malaria patients in our environment, we, therefore, hypothesize that malaria parasitemia affects some predictive inflammatory markers such as PLR, MNR (monocyte-to-neutrophil), MLR, NLR, Systemic Immune-inflammatory Index (SII) and Mean Platelet Volume (MPV) obtained from blood cell count [14]. Hence this study aims to examine the impact of the levels of malaria parasitemia on some predictive inflammatory markers obtained from the blood cell count of malaria patients in Benin City, Nigeria.

METHODS

Study Population

A total of 400 malaria patients with appropriate clinical findings and laboratory confirmation, who applied to the outpatient clinics or were hospitalized at the Benin City Central Hospital, Nigeria, were included in this study. Informed consent was obtained from all participants from whom data on socio-demography were obtained with the aid of a well-structured questionnaire. The study included all malaria-infected individuals who presented with both clinical symptoms and laboratory-confirmed malaria parasite infection. At the same time, those who refused to give permission were excluded. The ethical approval was obtained from the Ethics and Research Committee of Edo State Ministry of Health, Benin City, Nigeria.

Specimen Collection

Blood samples (5 mL) were collected from each study participant and dispensed into EDTA container used for malaria microscopy and Full Blood Count Analysis.

Malaria Microscopy

Malaria was diagnosed using Ogefere's method of examining stained thick blood films [14]. In brief, each blood specimen was used to make a thick and thin film and stained in 10% Giemsa stain for 30 minutes. The film was examined microscopically with an oil immersion lens, with 200 fields evaluated for each film. The level of parasitemia was grouped into high, moderate, and low, as previously described by Kotepui et al. [15] Briefly, the levels of malaria parasitemia data were grouped into high parasitemia (>10 parasite/oil field), moderate parasitemia (1–10 parasite/oil field), and low parasitemia (1–100 parasite/100 oil field).

Complete Blood Count

The white blood cell counts and platelet counts of all patients were done using a hematology auto analyzer (Sysmex K2IN, Sysmex Corporation, Kobe, Japan) by following the manufacturer's instructions.

Inflammatory Markers

Some basic inflammatory markers such as Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), Monocyte/Neutrophil Ratio (MNR), Mean Platelet Volume (MPV), Monocyte/Lymphocyte Ratio (MLR), and Systemic Immune-inflammatory Index (SII) were calculated from the obtained parameter of the Full Blood Count.[16] Briefly, NLR was calculated as the ratio of the neutrophils count to Lymphocyte counts; PLR was calculated as the ratio of the platelets count to Lymphocyte counts;, and MLR was calculated as the ratio of the monocytes count to Lymphocyte counts. The SII was defined as follows: SII=neutrophil x platelet/lymphocyte.

Statistical Analysis

The data obtained were analyzed using the chi-square ($\chi 2$) test, Student t-test, ANOVA and correlation using the statistical software Graph Pad INSTAT version 2.05 for Windows 7 (Graph Pad Software, La Jolla, California USA).

RESULTS

There were 166 females and 234 males among the 400 microscopically verified malaria parasites selected for the study. Table 1 shows the demographic characteristics of malaria patients about their parasitemia levels. Low parasitemia was seen in 114 (68.7%) of the 166 female malaria patients and 164 (70.1%) of the 234 male malaria patients. The incidence of parasitemia levels among malaria patients did not differ significantly between males and females (p=0.7189). The other demographic factors evaluated in this study had no significant impact on parasitemia levels among malaria patients, as presented in Table 1.

Eosinophils percentage count was significantly higher in individuals with high parasitemia (2.73±0.42%) than moderate parasitemia (2.16±0.22%) and low parasitemia (1.71±0.12%) (p=0.0121). There was no significant difference in the other white blood cell count and immune-inflammatory marker across the different levels of parasitemia (Table 2). Although SII was remarkably higher in patients with high parasitemia levels than the other parasitemia levels, this was not statistically significant (p=0.0753) (Table 2).

There was a significant correlation between most immune-inflammatory markers and malaria parasite density of malaria patients (Table 3). Apart from the MPV that does not correlate with the malaria parasite density, the other immune-inflammatory markers were significantly correlated in the following order MLR (r=0.322, p<0.0001), MNR (r=0.241, p<0.0001), NLR (r=0.122, p=0.015), SII (r=0.115, p=0.022) and PLR (r=0.109, p=0.030) (Table 3). MLR has the strongest positive correlation with malaria parasite density amongst all the inflammatory immune markers examined in this study.

DISCUSSION

Malaria is a highly inflammatory disease that necessitates complex interactions between host, parasite, and environmental variables in its pathogenesis [17]. The human response to malaria comprises a wide range of activities, including both cell-intrinsic and systemic pathways, but non-specific reactions drive the initial responses in a naive host [18]. Although extensive research is underway to uncover reliable predictors of malaria exposure, infection susceptibility, and the development of severe sequelae, this study aims to investigate the association between some predictive inflammatory markers and *P. falciparum* malaria.

The eosinophilic counts in this study were significantly higher in patients with high malaria parasitemia (p=0.0121) than patients with low and moderate malaria parasitemia. Although there are several reports of low eosinophils count, especially in malaria cases, the higher eosinophilia in patients with high malaria parasitemia in our study is in tandem with the earlier reports, which increased eosinophil activity in acute *Plasmodium falciparum* infection and marked eosinophilia with high parasitemia [19]. Our findings buttress the role of eosinophils as cytotoxic cells against parasitic infection. Therefore, increasing malaria parasite levels in the host can stimulate the copious production of eosinophils by T-helper cells immune cytokines, especially at the acute phase of malaria infection [19].

Table 1: Demographic Data of Malaria Patients in Relation to Parasitemia level.

Characteristics	No of Cases	Low	Moderate	High	p-value
Gender (Male)	234	164 (70.1)	54(23.1)	16(6.8)	0.7189
Age					
1-8 years	62	43(69.4)	17(27.4)	2(3.2)	
9-16 years	90	59(65.6)	19(21.1)	12(13.3)	
17-24 years	84	57(67.9)	21(25.0)	6(7.1)	
25-32 years	74	54(73.0)	18(24.3)	2(2.7)	0.4943
32-40 years	33	23(69.7)	6(18.2)	4(12.1)	
40-48 years	26	19(73.1)	6(23.1)	1(3.8)	
49-56 years	17	15(88.2)	1(5.9)	1(5.9)	
56-64 years	6	2(33.3)	2(33.3)	2(33.3)	
>65 years	8	6(75.0)	1(25.0)	1(25.0)*	
Non-formal Education	118	82(69.5)	30(25.4)	6(5.1)	
Primary Education	81	55(67.9)	16(19.8)	10(12.3)	0.6913
Secondary Education	130	90(69.2)	29(22.3)	11(8.5)	
Tertiary Education	71	51(71.8)	16(22.5)	4(5.6)	
Marital Status					
Married	114	78(68.4)	27(23.7)	9(7.9)	0.9826
Single	271	189(69.7)	61(22.5)	21(7.7)	
Others	15	11 (73.3)	3(20.0)	1(6.7)*	
Residential Area					
Rural	18	12(66.7)	5(27.8)	1(5.6)	0.8772
Sub-Urban	28	21(75.0)	6(21.4)	1(3.6)	
Urban	354	245(69.2)	80(22.6)	29(8.2)	
Living at A Flat	337	235(69.7)	76(22.6)	26(7.7)	
Living at One room	20	17(85.0)	2(10.0)	1(5.0)	0.2183
Living at Two room Self-contain	43	26(60.4)	13(30.3)	4(9.3)	
Malaria prevention Method					
Insecticides	244	172(70.5)	53(21.7)	19(7.8)	
Mosquito rep	10	7(70.0)	3(30.0)	0(0)*	0.9932
No Prevention method use	7	4(57.1)	2(28.6)	1(14.3)	
Prophylaxis	15	9(60.0)	6(40.0)	0(0)*	
Treated Net	124	86(69.4)	27(21.8)	11(8.9)	

*Not included in data analysis

Table 2: White Blood Cell Count and Immune-Inflammatory Markers of Malaria Patients on Artemisinin Therapy in Relation to levels of parasitemia.

Parameters	Levels of Parasitemia			P-Value
	Low (n=278)	Moderate (n=91)	High (n=31)	
White Blood Cell Count (/µL)	7325.54±250.83	6928.57±405.36	7548.39±892.14	0.6748
Lymphocyte count (%)	40.74±1.20	41.06±1.90	36.94±3.34	0.5629
Monocyte count (%)	8.11±0.25	8.97±0.97	7.44±0.62	0.3258
Neutrophil count (%)	48.87±1.23	46.01±2.07	53.90±4.12	0.1699
Eosinophil count (%)	1.71±0.12*	2.16±0.22	2.73±0.42*	0.0121*
Basophil count (%)	0.76±0.05	0.70±0.06	0.64±0.08	0.6127
Platelet count (x10^3/µL)	203.15±6.85	199.89±12.68	184.26±14.54	0.6770
NLR	1.99±0.13	1.66±0.18	2.53±0.46	0.1259
MNR	0.25±0.01	0.26±0.04	0.24±0.02	0.8995
PLR	6.74±0.37	5.66±0.45	7.31±1.23	0.2339
MLR	0.25±0.02	0.54±0.27	0.20±0.03	0.1431
MPV	8.03±0.29	7.78±0.53	7.01±0.70	0.5191
SII (x10^9cells/L)	399.90±302.03	294.22±312.67	493.36±110.25	0.0753

*Significant at P<0.05

Table 3. Correlation of Immune-Inflammatory Markers of Malaria Patients to malaria parasite density.

Immune-Inflammatory Markers	Correlation co-efficient (r)	P-value
Neutrophil/Lymphocyte Ratio	0.122	0.015
Monocyte/Neutrophil Ratio	0.241	<0.0001
Platelet/Lymphocyte Ratio	0.109	0.030
Monocyte/Lymphocyte Ratio	0.322	<0.0001
Mean Platelet Volume	0.030	0.547
SII	0.115	0.022

Our study revealed that the levels of malaria parasitemia did not significantly affect the white blood cell count and the differential count (apart from the eosinophil), and the inflammatory immune markers of the malaria patients. This finding is contrary to the earlier reports of Kotepui et al., who reported a significantly increased white blood cell count and neutrophils count with an increase in parasite density and a significant reduction in platelet, lymphocyte, and monocyte count with an increase in parasite density [15].

Furthermore, although hematological alterations as a result of malaria infection, such as anemia, thrombocytopenia, and leukocytosis or leukopenia, are well documented, these changes vary with the degree of malarial endemicity, confounding hemoglobinopathy, nutritional status, demographic factors, as well as malaria immunity which were not evaluated in this study [15].

In our study, NLR was discovered to positively correlate with malaria parasite density (r=0.122, p=0.015). This finding agrees with previous reports of Wolfswinkel et al. that discovered that the NLR correlated with parasitemia in imported malaria patients [20]. Also, the findings of Berens-Riha et al. are similar to our findings and Hermansyah et al., who reported that NLR was highest in severe falciparum malaria compared to uncomplicated falciparum. NLR was proposed as a marker for stress and inflammation. Therefore, the higher the levels of malaria parasitemia, the higher the induced stress and inflammation level [8,21].

Also, MNR was observed to have a strong significant positive correlation with malaria parasite density (r=0.241; P<0.0001). Although a previous study has associated monocyte to neutrophil ratio with severe malaria, especially in semi-immune patients, Tangteerawatana et al. reported a significant negative correlation of MNR with malaria parasitemia which is not in tandem with our findings [8,22]. Although the immune status of the patients in our study was not known, the positive correlation of the MNR to parasite density suggests that there was a very high immune response of the patients to inflammation caused by malaria parasite infection.

We observed that MLR has a robust positive correlation with malaria parasite density (r=0.322; P<0.0001), and this finding is similar to the findings in previous studies [8,23,24]. Furthermore, Antwi-Baffour et al. showed that increased monocyte to lymphocyte ratio correlates positively with increased parasitemia among children up to five years. They carried out their research amongst the general population like ours, and they discovered that MLR correlates positively with malaria parasite density [23,24]. Although malaria has a significant effect on the immune system and its components, the ratio of monocyte to lymphocyte (MLR) could be used to assess the ability of the immune response to handle malaria infection reliably. It could also be useful in determining the severity of malaria infection.

Although platelet count has been established to correlate with malaria parasitemia negatively, the PLR correlated positively with the level of malaria parasitemia in our study (r=0.109; p=0.030), which suggests that PLR can also be used as a criterion indicating subclinical inflammation. In addition, although there are limited data on the relationship between PLR and malaria infection, PLR has been indicated as a prognostic factor in some cancers and cardiovascular diseases [25].

Though various studies have shown that MPV, which is one of the markers used in the evaluation of platelet size, is also used for the evaluation of both systemic inflammatory activity and response to treatment, the MPV in our study did not show any relationship with malaria parasitemia (r=0.030, p=0.547) [26]. Zareifar et al.'s study showed a high platelet count and low MPV in the active period of inflammation and infection. Therefore, they suggested that both are reliable markers of inflammation. Our finding is similar to the findings of Sula and Tekin, who found no significant difference in the MPV level in patients with leishmaniasis [26,27]. Therefore, it suggests that MPV may not be a marker of inflammation in parasitic infection.

Systemic immune-inflammation index, platelet, and lymphocyte counts have been recently suggested to be associated with poor outcomes in various types of cancers [29]. The SII in our study had a significant positive correlation with the levels of malaria parasitemia (r=0.115, p=0.022). According to our knowledge, our study is the first to establish the relationship between malaria parasitemia and this relatively novel inflammatory marker. In addition, available data have established that high SII may be a potential prognostic marker in patients with various cancers and associated with poor overall outcomes such as hepatocellular carcinoma, oesophageal squamous cell carcinoma, and small cell lung cancer [28].

In conclusion, our study has demonstrated a positive correlation between malaria parasite density and most inflammatory immune markers. Furthermore, this research has provided evidence that some of these predictive markers of inflammation can be used in resource-limited settings in assessing malaria severity.

Our study had several limitations. Firstly, we did not include malaria-negative controls in our study to compare these inflammatory markers in non-malaria patients. Secondly, monitoring was not done for the patients to compare the levels of these inflammatory markers after they

were treated for the *P. falciparum* infections. Thirdly, there are no established reference ranges for these inflammatory markers in our locality. Finally, because we did not investigate the presence of co-infections in our cross-sectional survey, future research will need to look into the impact of probable helminth, bacterial, or viral co-infections on the link between these inflammatory markers and clinical malaria.

However, our study has revealed an association between NLR, MNR, MLR, PLR, and SII with malaria parasitemia. We recommend that there is a need for the evaluation of these markers of inflammation as a cost-effective way of assessing malaria severity as well as for malaria prognosis since some other biomarkers are quite expensive and non-accessible in low-income areas. Also, they could be useful effective treatment and control of malaria since they are all positively correlated with malaria parasite density.

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