Patterns of Mannose-Binding Lectin (MBL) responses to *Plasmodium falciparum* infections in hyperendemic settings

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Availability of data and materials: the data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Summary

Background: malaria caused by *Plasmodium falciparum* remains a significant and major public health concern in Africa, particularly in hyperendemic regions. Recurrent fevers and high quantities of inflammatory mediators in the circulation define the disease's blood stages. By binding to non-self-pathogen oligosaccharide surfaces, Mannose-Binding Lectin **(**MBL) and lectin complement pathways trigger innate immune processes and contribute to the formation of adaptive immune responses.

Methods: in Sudan, we investigated the varied immune response levels of MBL to the different phases of *P. falciparum* infection in White Nile and Blue Nile states endemic to malaria. And we looked at the interaction of regulatory Interleukin 6 (IL-6) cytokines on MBL during infection. Our study was based on a total of 108 cases, in which 86 patients (62.0%) were uncomplicated and (17.6%) were severe, all met the diagnostic criteria and were clinically admitted for malaria infections. For the determination of serum MBL and IL-6 levels, a commercial ELISA kit was employed.

Results: the analysis of the results revealed significantly elevated levels of MBL and IL-6 in both severe and uncomplicated cases ($p<0.001$). And MBL average in contrast to residents, Blue Nile patients had high parasitemia (599.9 ng/mL) and this difference was statistically significant (p-value<0.05). The remarkable positive correlation of IL-6 serum levels with MBL among malaria patients and healthy controls ($r=0.399$, $p<0.001$) was noted too.

Conclusions: according to the findings of this study, patients living in hyperendemic areas exhibit a different MBL response rate and appear to be more homogeneous in proportion to the density of *P. falciparum* due to parasitemia. In addition, it is also dependent on the regulatory immune mediator IL-6.

Introduction

Malaria is one of the world's worst infectious diseases, along with HIV and tuberculosis, causing more than one million deaths worldwide, especially in sub-Saharan Africa [5]. The four most frequent Plasmodium species that cause human infections are *Plasmodium vivax, Plasmodium falciparum, Plasmodium ovale, and Plasmodium malaria. P. falciparum* is the most powerful and deadly evolutionary selection force in the most recent history of the human genome [8]. This is because it often leads to death from malaria, which usually affects young children under the age of 5 and pregnant women [23]. The blood phase of malaria is charac-

terized by high levels of inflammatory mediators in the blood and periodic high fevers. The occurrence of cerebral malaria, as well as chronic and excessive inflammation caused by *P. falciparum* infection and severe malarial anaemia, are additional causes of sequelae of P. falciparum infection [18].

Malaria immunity is intricate and largely both species and stage-specific. The main immune response to protozoa is phagocytosis, although some of these parasites are resistant to it and may reproduce inside macrophages [33]. Mannose-Binding Lectin (MBL) is a member of the collectin protein family and a component of the innate immune system with the ability to recognize patterns. It is also thought to have an impact on the effectiveness of the immune response [3]. The complement system is activated by the interaction of MBL polymers with serine proteases. Pathogen opsonization and phagocytosis are made easier by them. MBL detects immunogenic *P. falciparum*-infected erythrocyte proteins in humans [16]. The mannose-binding lectin consists of six trimeric components and is structurally like C1q [19].

The level of MBL in plasma can vary widely. MBL is associated with a variety of clinical parasites. Low blood levels of MBL are caused by three polymorphisms in MBL2 (structural genes) and two polymorphisms in MBL promoter genes [35,20]. Allele A represents the wild-type allele, whereas allele O represents the variant alleles B, C, or D. Variants B (rs1800450), and C (rs1800451), and D (rs5030737) are three Single Nucleotide Polymorphisms (SNPs) at codons 52, 54, and 57 of exon 1. Furthermore, SNPs in the promoter domain at locations -221, and -550, identified as variants H/L (rs11003125) along with X/Y (rs7096206), were discovered too [22,15].

The presumption that: "High MBL levels in serum render protection, while low levels raise the likelihood of disease" has been made due to the key activities of MBL in the immune defense mechanism [27]. Several clinical studies have shown that MBL deficiency is associated with infection risk induced especially by extracellular pathogens [9,34]. As children age, the importance of MBL tends to diminish because maternal immunity has waned, but acquired immunity has not fully developed. in adults, MBL seems to be restricted to immunosuppression-related conditions [25].

Interleukin 6, a regulatory or anti-inflammatory mediator, has been linked to severe illness and is greatly elevated after malaria infection [4,2]. Infected erythrocytes are identified by macrophages, which produce IL-6 as early as the ring stage. IL-6 promotes the production of acute phase proteins in the liver through binding to interleukin 6 responsive regions in gene promoters, which are critical for their expression. [6]. There has been evidence of putative IL-6-MBL interactions in the pathophysiology of numerous disorders due to the presence of some type 1 and type 2 IL-6-responsive sequences found in the human MBL2 promoter region [32].

Severe Malaria (SM) is a potentially fatal complication that is especially common in areas of high transmission in Africa. The clinical appearance of severe malaria is influenced by both age and intensity of exposure [7]. We aimed to investigate the discrepancies in MBL response to *P. falciparum* infection at different intensity levels, which may be influenced by regional malaria endemicity. Furthermore, we sought to explore whether MBL levels in endemic regions may reflect malaria pathogenicity and severity, as well as providing information on how IL-6 affects MBL as an active protein phase and the manner of regulation during *P.falciparum* infection [14,10].

Materials and Methods

Study design and study population

Cross-sectional research was carried out in two states, White Nile, and Blue Nile, which have the highest endemicity and persistent transmission in the southern region of Sudan, from Mid-March to July 2021. The Sudanese patients with *P. falciparum* infection were the target, infected patients recruited to this study were admitted to National Health Insurance treating centers in both states, and we excluded those infected individuals with any immunological disorders. The study population have common ethnical categories and was grouped according to the geographic distribution of infections, age group (adults and children) and sex (Table 1).

Sampling and preparation

Authorization was obtained from the National Health Insurance Administration, as well as informed permission from the treating physicians, and each volunteer or patient was informed of the purpose of the study. During the study period, 108 patients were enlisted, and blood was collected from all subjects. Five mL of whole venous blood were collected first, and then two mL of plasma were separated for serological testing. Individuals in the case group were infected with *P. falciparum* (N=86) (White Nile 46, Blue Nile 40), while those in the control group were healthy individuals who tested negative for *P. falciparum* (N=20).

Parasitological analysis

The immunochromatography assay relied on the first detection of HRP-II in *P. falciparum* malaria, and the reference screening criteria were used. Thick blood stains were generated for all tested samples, labeled, and then dyed for 10 minutes with Giemsa stain 10% (pH 7.2), on a clean slide before being studied at x100 magnification using an optical microscope. Positive results on thick smears are scored using the "plus" system score: (if (1 to 9 trophozoites in 100 fields) that +;(1 to 10 trophozoites in 10 fields) that ++; +++ means (1 to 10 trophozoites per field); and for (more than 10 trophozoites per field) reported as ++++). Also, the infection by

Table 1. Distribution of demographic among patients with malaria and healthy control.

Characteristics		Uncomplicated malaria (n=67) (62.0%)	Severe malaria (n=19) (17.6%)	Control group (n=22)	chi^2, p-value
Age group n (%)	<5	53 (79.1)	15 (78.9)	22 (100)	5.53,
	≥5	14 (20.9)	4 (21.1)	0	0.063
Gender n (%)	Male	43 (64.2)	9 (47.4)	11 (50.0)	2.51,
	Female	24 (35.8)	10 (52.6)	11 (50.0)	0.285
Residence n (%)	While Nile	37 (55.2)	9 (47.4)	-	0.367,
	Blue Nile	30 (44.8)	10 (52.0)	-	0.545

A p-value>0.05 was not considered statistically significant.

P. falciparum species was verified using thin blood slide smears to the red blood cell-infected per * 100 cell fields.

Measurement of Mannose-Binding Lectin and Interleukin-6

Venous blood from study participants was drawn into EDTA from study participants upon admission to National Health Insurance Administration facilities. Plasma was obtained from blood after centrifugation and kept at -80°C. MBL and IL-6 were measured in plasma using an automated ELISA Mindray MR-96A and a competitive sandwich enzyme immunoassay method according to the manufacturer's instructions (ELK Biotechnology, Wuhan, China). The MBL detection range of the assay was 6.25-400 ng/mL with a sensitivity of 2.45 ng/mL, while the IL-6 detection range was 7.82-500 pg/mL with a sensitivity of 3.2 pg/mL. We were able to quantify the amounts of Anti-Mannose Binding Lectin Antibody (Anti-MBL) and Interleukin 6 (IL6) in the samples by comparing their OD with the reference curve.

Statistical analysis

Stata version 14 (Stata Corp, College Station, USA) software was used for statistical analyses. In the descriptive analysis, the visual display of data in figures and tables gives demographic and clinical data in numbers, percentages, and figures. This is a clear indication of the distribution and relationships of the people. The chi-square test was used to determine categorical variables. Continuous variable comparisons were performed using the one-way analysis of variance ANOVA for parametric data, the student t-test for parametric data, and the Mann-Whitney rank sum for nonparametric data. The Pearson correlation coefficient was used to calculate the relationships between MBL, and IL-6 blood levels. In all statistical comparisons, an alpha value of 0.05 represented a statistically significant difference.

Results

In this study, an overall of 108 study subjects were recruited. There were eighty-six patients diagnosed with malaria, 62.0% were uncomplicated, and 17.6% were severe. Their average age was 3.25, ranging from 1 to 9 years old. The gender distribution was 52.6% females and 47.7% males diagnosed with severe malaria. Patients from White Nile were more frequent (55.2%) than other groups. All these differences are not statistically significant (p-value >0.05).

Significantly elevated levels of MBL (640.0 ng/mL *versus* 138.5 ng/mL; p<0.001) and IL-6 (29.0 pg/mL *versus* 5.5 pg/mL; p<0.001), were noted in severe cases *versus* healthy controls. No association was observed between MBL and IL-6 levels among severe and uncomplicated malaria patients (p>0.05). Significantly elevated levels of MBL (600.0 ng/mL *vs* 138.5 ng/mL; p<0.001) and IL-6 (25.0 pg/mL *versus* 5.5 pg/mL; p<0.001) were noted in uncomplicated malaria *versus* healthy controls (Table 2, Table 3).

According to the residents, the study examined the concentrations of MBL to malaria parasitemia. The average of patients from Blue Nile had high parasitemia (599.9 ng/mL), and this difference was statistically significant (p-value <0.05). No significant association was found between parasite density and White Nile patients.

We reported that the average of MBL based on a residence region has oscillated in varying degrees between White Nile and Blue Nile-infected individuals, The mean of MBL in the acute phases was considerably enhanced gradually depending on parasite density for those patients from the Blue Nile state and differed from the diverse growing of MBL in White Nile infected patients, according to our findings (Figure 1).

The study group found that the median MBL levels overlapped with gender among the age groups. There was no difference between genders for this parameter among age groups (p=0.05) (Figure 2). The study group showed that the median IL-6 serum level overlapped with gender among children. This level of IL6 serum level showed no significant difference (p-value >0.05) (Figure 3).

Notably, IL-6 serum levels were positively correlated with MBL (r=0.399, p<0.001) in combined control groups (Figure 4).

Discussion

Recently, the relevance of the immune response in both innate and specific immunity to *P. falciparum* infection has been empha-

Table 2. Mannose-Binding Lectin (MBL) and Interleukin 6 (IL6) results between matched severe *P. falciparum* malaria, uncomplicated malaria, and healthy control.

	Severe malaria median (range)	p-value[a]	Uncomplicated malaria median (range)	p-value[b]	Control median (range)	p-value[c]
MBL (ng/mL)	640.0 (213.0-1600.0)	<0.001*	600.0 (158.0-1400.0)	0.086	138.50 (213.0-1600.0)	<0.001*
IL6 (pg/mL)	29.0 (8-1146.0)	<0.001*	25.0 (3-2173.0)	0.708	5.50 (2.0-9.0)	<0.001*

*Significant value as figured out by student t-test and Mann-Whitney rank sum analysis with a level of significance set at p<0.05.
[a]Severe *versus* healthy; [b]Severe *versus* uncomplicated; [c]Uncomplicated *versus* healthy

Table 3. Comparison of parasite counts concerning Mannose-Binding Lectin (MBL) according to residence.

Parasitemia	Total average of MBL (range)/ng/mL	White Nile mean (range)/ng/mL	Blue Nile mean (range)/ng/mL
Low (+)	631.43 (168.0-850.0)	658.46 (460.0-810.0)	587.50 (168.0-850.0)
Intermediate (++)	480.69 (158.0-820.0)	610.29 (339.0-820.0)	297.08 (158.0-389.0)
Slightly high (+++)	593.94 (182.0-1400.0)	757.14 (420.0-1400.0)	479.70 (182.0-810.0)
High (++++)	668.37 (213.0-1600.0)	744.44 (470.0-1600.0)	599.90 (213.0-830.0)
F-test, p-value	2.78, 0.046	1.068, 0.373	4.933, 0.006*

*p-value<0.05 was considered statistically significant.

sized. Toll-Like Receptors (TLRs), NO inducible synthase, IFN receptors, and TNF-alpha are examples of native immune mediators that have been demonstrated to contribute efficiently against malaria or are mediated by sequential and coordinated responses. MBL binding is one of three key pathways of complement activation [12], and has important functions as the first line of defense against malaria infection [26]. MBL multiplicity of its possible targets stems from the specificities of its carbohydrate recognition followed by opsonization and/or complement activation via the lectin pathway [31].

We investigated whether MLB responses to *P. Falciparum* infection vary according to the intensity of the parasite infection and are spatially impacted by the disease's endemic prevalence. We discovered substantial increases in MBL levels in severe cases and uncomplicated malaria patients compared to healthy controls by reporting the range of blood circulating MBL in our patients (Table 2). The findings in this investigation supported that MBL performs a similar function in the elimination of the *P. Falciparum* parasite as well as other infectious disorders [25] before a specific adaptive immune response occurs and eliminates more advanced stages of malaria infection.

Something noteworthy about this discovery and its implications for the immune system's engagement with *P. Falciparum*. The levels of 'active' MBL in parasitemia have been observed to change in various degrees, which gives an indication of the relation with the infection intensity level in the region [29]. MBL levels increased in patients with uncomplicated malaria during the primitive infection stage (Table 3), then fell in the following phase of infection, and then increased in the next advanced phases, until they reached substantial levels in complex "severe" malaria patients [21]. MBL levels differed significantly and might depend on the endemic residential zone.

And considering the MBL average changes in response to the density of the plasmodium parasite. We found that cases of malaria in the Blue Nile condition of hyperendemic transmission in South Sudan [17,1] showed a significant difference in mean body burden level with parasitemia intensity (Figure 1), and by considering recurrent infection and/or high exposure to infection rates [21,13]. It appears that these changes are more homogenous in response to

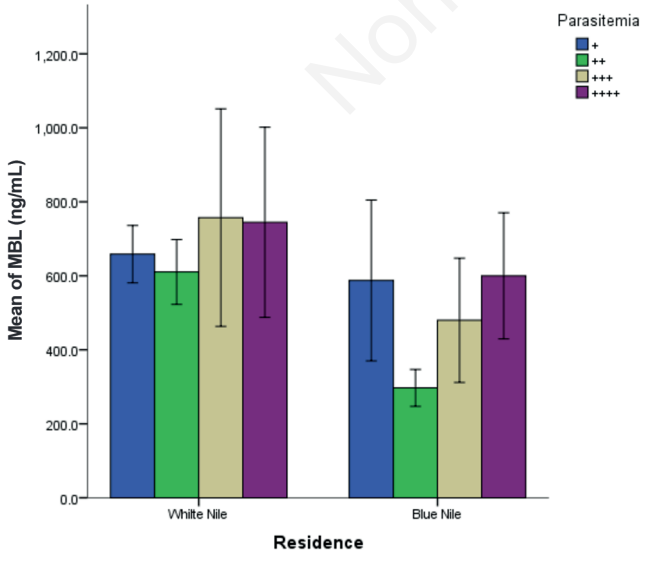

Figure 1. Distribution of Mannose-Binding Lectin (MBL) among infected residents in endemic areas.

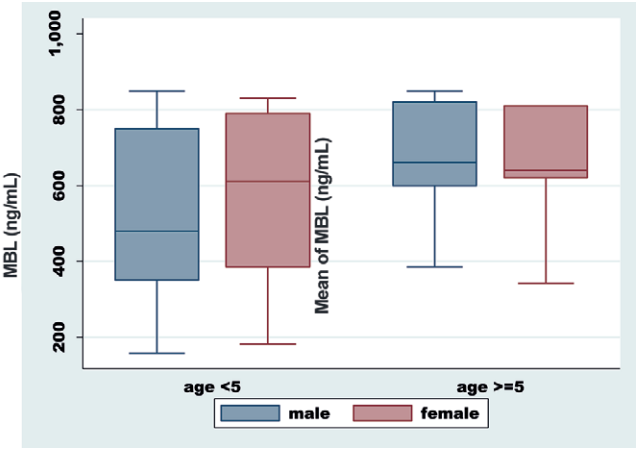

Figure 2. Box plot showing the distribution Mannose-Binding Lectin (MBL) level with age group among gender.

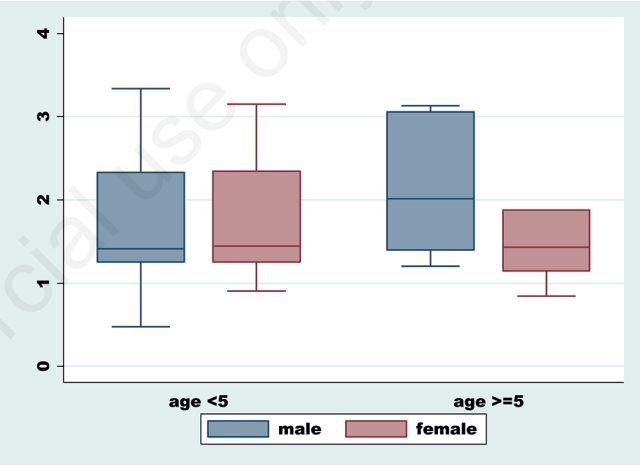

Figure 3. Box plot showing the distribution of Interleukin 6 (IL-6) serum level with age group among gender.

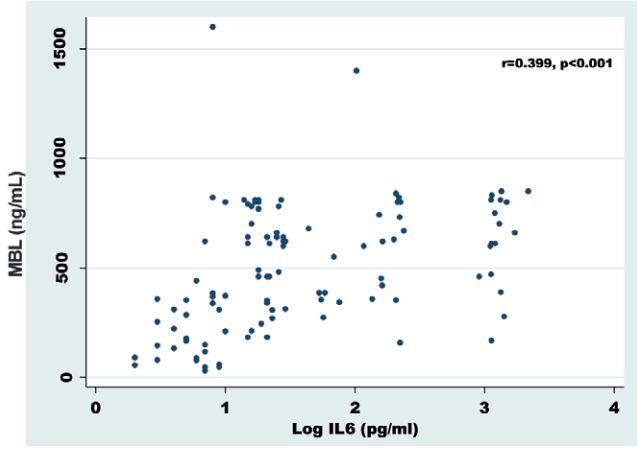

Figure 4. Correlation analysis of Interleukin 6 (IL-6) serum levels with Mannose-Binding Lectin (MBL) among malaria patients and healthy controls.

malaria infection and therefore may reflect the better immunogenicity resistance status of those patients. Moreover, despite the substantial overlap in MBL and IL-6 medians, we were unable to locate any serious discrepancies according to gender among age groups (Figure 2, Figure 3) [28].

In addition, we detected an association between circulating levels of MBL and the regulatory and proinflammatory cytokines IL-6 [24] in inflammatory responses during *P. Falciparum* infection (Figure 4). We found a positive association between malaria patients and healthy controls by estimating MBL and IL-6 levels and comparing them with parasite densities in both circulating states, which is consistent with previous work showing that IL-6 specifically regulates and contributes positively to the acute phase protein synthesis in human hepatocytes [24,11]. However, the precise mechanism behind the favorable tandem of MBL with IL-6 demands additional investigations. In addition, it is not clear whether these results also represent the pathogenicity of malaria infections in endemic areas.

Conclusions

In summary, we report here the distinct and efficient participation of MBL in *P. Falciparum* infection, which depends on parasite intensity and could be influenced geographically by malaria disease's endemic occurrence, especially in a hyperendemic setting. Enabling infected individuals to control the severity of their current infection and/or future re-infections. In addition to facilitating parasite clearance by inflammatory function, lectin is also involved in feedback on the advanced immune response as the active protein phase that is regulated by other inflammatory mediators, including IL-6, which contributes to more effective inflammatory strategies for treating and preventing malaria infection.

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