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Patterns of Anti-Malarial Immunoglobulin E Responses and Membrane Expression of the FcεRI Complex in Malaria

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Abstract

Background: FcεRI, also known as the high-affinity immunoglobulin E (IgE) membrane receptor, is a receptor that binds to the Fc fragment of IgE antibody. It is expressed on the surface of mast cells, basophils, eosinophils, and has recently been discovered in neutrophils, particularly in asthmatics. Several experimental studies have demonstrated the presence of FcεRI on the surface of these neutrophils. Other studies are underway to determine a possible correlation between plasma IgE and Polymorphonuclear neutrophile-FcεRI (PMN-FcεRI). Similarly, research is ongoing for the study of the profile of IgE in severe malaria. **Objectives:** To evaluate plasma IgE responses to *P. falciparum* Merozoite Surface Proteins and assess their relationship with neutrophil FcεRI membrane expression and surface-bound IgE (PMN-IgE) across disease severity and clinical outcomes in malaria patients. **Methodology:** Plasma IgE were determined by the Enzyme Linked Immunosorbent Assay (ELISA) method to 107 patients (adults and children) recruited in 2013, 2014, and 2015. PMN-FcεRI and PMN-IgE were compared according to malaria severity and outcome. **Results**: No correlation was found between FcεRI expression and plasma IgE titers. PMN-FcεRI were higher in patients with Cerebral Malaria (CM) than in those with Uncomplicated Malaria (UM), as well as in those who died from the disease. **Conclusion:** These findings regarding anti-MSP IgE shed light on the complex relationship that may exist between PMN-FcεRI, PMN-IgE, and plasma IgE. This study also highlights the significant impact that the pathological context can have on the components of the innate immune system. We recommend future studies to use whole merozoite extracts for more comprehensive IgE measurement and apply "Omics" technology to explore the broader immune response environment. This approach could provide deeper insights into the role of IgE-mediated neutrophil responses in cerebral malaria.

Keywords

Cerebral Malaria, FcεRI, Neutrophiles, Immunoglobulin E, *Plasmodium falciparum*

1. Introduction

Malaria is a febrile, haemolytic erythrocytopathy caused by the presence and multiplication in hepatocytes and then in erythrocytes of a haematozoan of the genus *Plasmodium*, transmitted to a vertebrate host by the bite of an infected female *Anopheles* mosquitoes. Five species of *Plasmodium* are capable of infecting humans: *Plasmodium vivax*, *P. malaria*, *P. ovale*, *P. falciparum and P. knowlesi* [1]. *P. falciparum* is responsible for severe forms of malaria, ranging from damage to vital organs such as the brain, to metabolic disorders that can lead to death [2]. Antimalarial immunity is a determining factor in the course and severity of the disease. Although protective immunity against severe malaria has long been attributed to IgG subclasses, the role of immunoglobulin E (IgE) in the pathophysiology of *P. falciparum* is attracting growing interest. Pioneering studies conducted by Perlmann *et al.* demonstrated that people living in malaria-endemic areas have significantly higher levels of total IgE antibodies and parasite-specific IgE antibodies, with the highest titers observed in patients with cerebral malaria [3]. These studies suggest that, whilst IgE may contribute to the elimination of the parasite, immune complexes containing excess IgE can cross-link with Fc-receptors, thereby triggering a cascade of pro-inflammatory cytokines such as TNF-α and nitric oxide, which exacerbates vascular inflammation and tissue damage [4]. Despite these fundamental observations, the specific role of IgE interaction with granulocyte membrane receptors; in particular the expression of FcεRI on neutrophils during cerebral malaria in humans; remains poorly understood. Experimental studies have highlighted the interaction between high-affinity FcεRI receptors and IgE, and have thus demonstrated their key role in hypersensitivity reactions [5]. A number of studies based on cellular and molecular biophysics have demonstrated IgE-FcεRI binding and interaction on the surface of neutrophils [6] [7]. Experimental studies in mouse models of cerebral malaria (*Plasmodium berghei* ANKA) demonstrated that neutrophil-associated FcεRI (Polymorphonuclear neutrophile-FcεRI) expression plays a pivotal role in disease pathogenesis, as FcεRI-deficient mice exhibited reduced susceptibility to experimental cerebral malaria [8]. While other previous studies in allergic asthma showed that neutrophil FcεRI expression is minimal and independent of circulating IgE levels [9], acute systemic infections such as cerebral malaria involve massive neutrophil activation [10], distinct cytokine signaling [11] and altered receptor dynamics. However, whether Polymorphonuclear neutrophile-FcεRI expression (PMN-FcεRI) and surface-bound IgE (Polymorphonuclear neutrophile-IgE) are upregulated during human cerebral malaria and correlate with specific antiplasmodial plasma IgE responses remains to be established. We hypothesized that

in the hyper-inflammatory setting of severe malaria—which differs from the allergic context of asthma the expression of PMN-FcεRI and Polymorphonuclear neutrophile-IgE (PMN-IgE) is differentially regulated according to malaria severity and clinical outcome, providing insights into the involvement of IgE-mediated neutrophil responses in malaria pathogenesis.

The aim of our study was to evaluate specific IgE levels against *P. falciparum* merozoite surface proteins (MSP1-p19 and MSP4-p20) in patients with cerebral malaria (CM), and to assess their correlation with flow-cytometric parameters of neutrophil activation specifically, the membrane expression of FcεRI receptors (PMN-FcεRI) and surface-bound IgE (PMN-IgE) across clinical severities (cerebral malaria/uncomplicated malaria) and patient outcomes (Deceased/Survivors).

2. Materials and Methods

2.1. Study Setting

At the Principal Hospital of Dakar, venous blood sample collection took place in the Intensive Care Unit (ICU), infectious disease unit and the laboratory where all biological tests for the patients studied were performed, except for immunological tests. Immunological analyses, such as antibody quantification, were conducted at the Immunology and Genetics Unit of the Faculty of Medicine, Pharmacy, and Odontology at Cheikh Anta Diop University in Dakar.

2.2. Type and Study Period

We conducted a descriptive study with an analytical components, recruiting patients with severe forms of malaria (cerebral malaria) (CM) admitted to the hospital services. Similarly, there are also some patients consulted for uncomplicated malaria (UM) syndrome which was taking part in recruitment. In addition, non infected individuals were recruited and designated as the control patients group (CP).

The choice of period was based on the high transmission level of the parasite, particularly due to the abundance of vectors (*Anopheles*). This increased the probability of obtaining positive samples for *P. falciparum*. Recruitment took place from July to November in the following years: 2013, 2014, and 2015.

2.3. Patient Recruitment and Selection Criteria

Patients were recruited based on World Health Organization (WHO) criteria and Saissy *et al.* studies for the different clinical forms of severe malaria requiring intensive care [12] [13]. Life-threatening CM was defined following the WHO criteria as the presence of *P. falciparum* in blood smears accompanied by a coma with no other cause of cerebral symptoms. UM cases were defined as those with positive blood smear for *P. falciparum* and having fever, and no other symptoms of CM [12]. CP come from healthy volunteers living in Dakar.

Malaria diagnosis was screened using a rapid diagnostic test (RDT) for *Plasmodium falciparum* antigen detection and confirmed by microscopic examination of thick and thin blood smears for parasite identification and quantification. This

study was approved by the Research Ethics Committee of Cheikh Anta Diop University in Dakar (protocol No. 001/2015/CER/UCAD).

Inclusion Criteria

During study periods, CM admitted to the ICU for severe malaria with a positive rapid diagnostic test (RDT) and confirmed by a positive thick blood smear and thin blood smear were included. These patients presented at least one severity criterion of malaria as defined by the WHO [12]. UM patients were recruited in the infectious disease unit during the same time-period. They were defined as having a positive RDT and blood smear for *P. falciparum* with fever and no symptoms of severe malaria. CP with negative thick blood smear; thin blood smear or a rapid diagnostic test (RDT) were also included.

Non-Inclusion Criteria

Patients were not included if they:

- Did not have a thick blood smear, thin blood smear or a rapid diagnostic test (RDT) at admission.
- Were known to be infected with pathogens such as Human Immunodeficiency Virus (HIV) and *Mycobacterium tuberculosis*.
- Did not provide consent.

Exclusion Criteria

CM patients were excluded from the study based on medical history, disease history, and potential co-morbidities that could interfere with the assays conducted in our investigations. Criteria includes: no stored sample, patients with gravid eclampsy in post pregnancy, septicemia (*S. Pyogenes*), pulmonary infection (*E. coli*, *S. pneumoniae*), gastro intestinal infection (*Salmonella*). UM patients were excluded because of: no consent from patient and no stored samples; pregnant patients; patients with acute infections associated with respiratory or intestinal infections, patients for whome data not available or insufficient. Samples with inadequate volume, hemolyzed blood, or those lost/damaged during long-distance transport and processing were systematically excluded from final analyses.

Out of 131 patients, only 107 considering exclusion criteria, were selected for the study. This includes 37 individuals consulting for a UM episode, 36 patients hospitalized for CM, and 34 CP.

2.4. Collection of Clinical and Biological Data

Data collection was performed using a questionnaire based on the admission form and patient file. We considered different criteria such as sociological and demographic characteristics (age, sex, admission), biological data (blood count, blood group-rhesus factor, thick blood smear, and parasite density), serological and immunological characteristics (immunological markers of neutrophils, levels of IgE antibodies).

2.5. Samples

For each patient, a venous blood sample was taken in a tube containing Ethylene-

diaminetetraacetic acid (EDTA), and the preparation of a thick blood smear, thin blood smear, or a rapid diagnostic test (RDT) at the time of recruitment allowed for the detection and/or assessment of parasite density. The blood was then divided into two parts:

- **First Part:** Used for the study of hematological data (complete blood count by an automated analyzer) and immunological data (by flow cytometry).
- **Second Part:** Centrifuged at 2000 rpm for 10 minutes, allowing for the isolation of plasma, which was then stored at −20˚C. These plasmas were diluted 1/100 at the time of IgE assays.

2.6. Antigens

Two recombinant antigens were studied; both proteins expressed on the surface of the *P. falciparum* merozoite.

Merozoite Surface Protein-1p19 Antigen

Our study focuses on MSP-1p19, which may play a crucial role in food vacuole biogenesis and function throughout the intra-erythrocytic phase [14]. The protein used was genetically engineered using the *Baculovirus*/insect cell expression system, reproducing the parasite protein's Epidermal Growth Factor-like (EGF-like) conformation developed by Longacre's team at the Pasteur Institute in Paris.

Merozoite Surface Protein-4p20 Antigen

For this study, we used the MSP-4 construct: a full-length protein (MSP-4p40) from which we obtained the 20 kDa C-terminal fragment containing the EGF domain (MSP-4p20). These proteins were produced at the Parasite Vaccine Laboratory of the Pasteur Institute in Paris using the *Baculovirus*/insect cell expression system [15].

2.7. Measurement of Serum Antibodies with Enzyme Linked Immunosorbent Assay and Data from Flow Cytometry

The determination of IgE levels directed against the studied antigens was conducted using Enzyme Linked Immunosorbent Assay (ELISA). Recombinant antigens were prepared in sterile phosphate-buffered saline (PBS) and used to coat Immulon-4 microplates at a final concentration of 0.5 µg/mL. Plasma samples were tested in duplicate at a 1:100 dilution, and IgE antibody levels were quantified by ELISA following procedures previously validated in similar immuno-epidemiological studies [16]-[18]. Antibody detection relied on mouse monoclonal antibodies specific for human isotypes (Cappel®, USA), followed by peroxidase-conjugated goat anti-mouse IgE (1:2000) (Sigma®, St. Louis, MO, USA), each used at optimized working dilutions after preliminary titration [18] [19]. To ensure inter-plate consistency, standardized reference controls were included in every assay. The positive control consisted of a pooled serum sample from clinically immune adults residing in Dielmo, a holoendemic malaria village in Senegal. Two negative controls were used: pooled sera from non-immune European donors and pooled sera from non-immune African individuals from

Dakar who tested negative for antibodies against *P. falciparum* schizont extract [15]-[18]. ELISA results were expressed as an optical density (OD) ratio, calculated as the OD of each sample divided by the OD of the naïve serum pool. Samples yielding an OD ratio greater than 2—which corresponds to the naïve control value plus three standard deviations—were classified as seropositive for prevalence analyses.

2.8. Cellular Study by Flow Cytometry

For flow cytometry, polymorphonuclear neutrophile cells (PMN) were isolated from peripheral blood (30 to 45 minutes after blood collection), counted, and then labeled with monoclonal antibodies anti-CD16/AF647, anti-CD49/FITC, anti-FcεRI/PE, anti-CD203/PerCP, and anti-IgE/PE in various combinations. Data acquisition by flow cytometry was performed using Cell Quest® software before analysis with FlowJo®10.0.6 according to the procedure shown in **Figure 1**. PMN were isolated via a sequential negative selection gating strategy within the polymorphonuclear cell gate. Briefly, polymorphonuclear basophils (CD203+) and polymorphonuclear eosinophils (CD49+) were systematically excluded by selecting CD203-CD49-polymorphonuclear, yielding a highly purified target PMN population for subsequent evaluation of surface FcεRI and IgE expression.

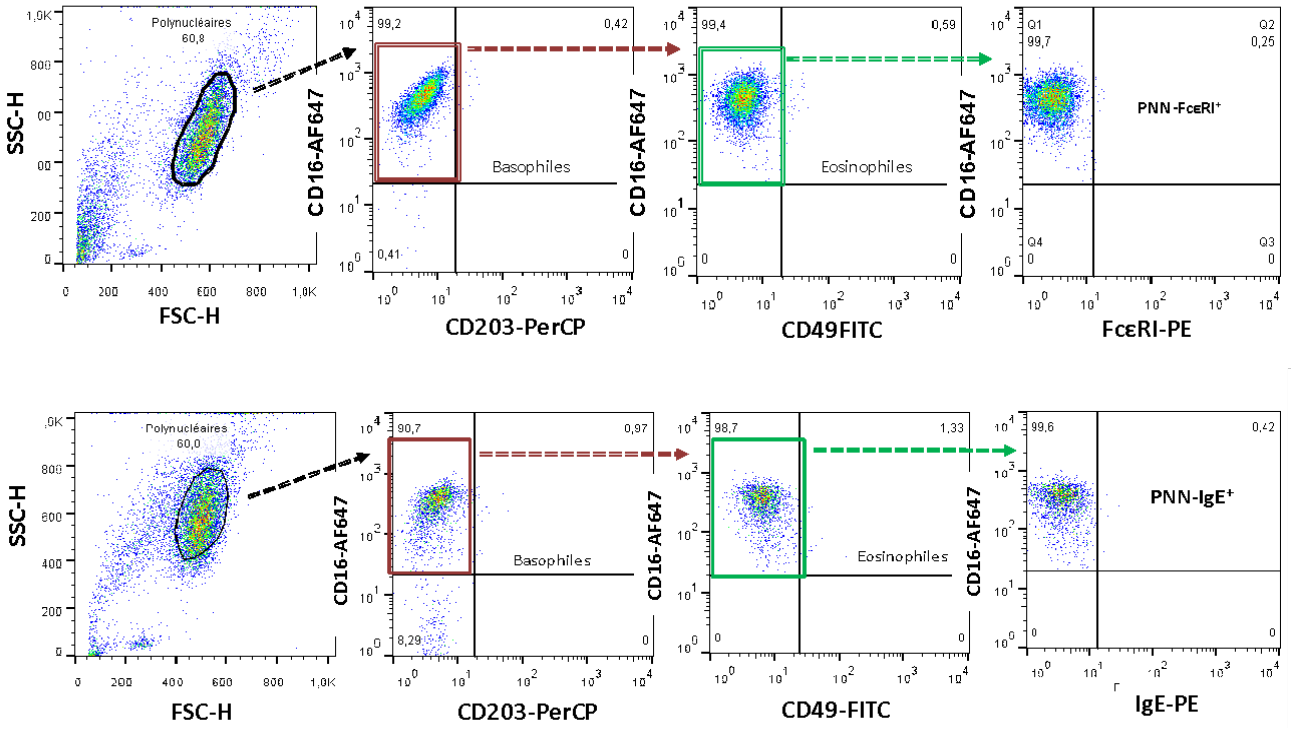


Figure 1. Plots for determining the proportions of polymorphonuclear-FcεRI and polymorphonuclear-IgE. Polymorphonuclear cells were first gated based on forward and side scatter properties (FSC/SSC). To isolate Polymorphonuclear neutrophils PMN through a negative selection gating strategy, polymorphonuclear basophils and polymorphonuclear eosinophils were sequentially excluded: basophils were removed by gating on the CD203-polymorphonuclear population, and eosinophils were subsequently excluded by selecting CD49-cells. The resulting purified neutrophil population (CD203-CD49-PMNs) was then analyzed for the frequency (%) of membrane FcεRI+ and neutrophil-bound IgE+ events.

2.9. Statistical Analysis

For statistical analysis, we utilized Statview 5.1 software (SAS Institute, Cary, NJ). Continuous variable distributions were verified to be non-Gaussian, thus non-parametric tests were chosen:

- Mann-Whitney and Kruskal-Wallis tests for unpaired comparisons,
- Wilcoxon signed-rank test for paired comparisons,
- Spearman's rank correlation tests to explore relationships between continuous variables.

A difference was considered statistically significant when the *p*-value was less than 0.05.

3. Results

3.1. Epidemiological and Clinico-Biological Characteristics of the Patient Cohorts

This study involved 107 patients divided into three groups:

- 36 Cerebral Malaria patients (CM)
- 37 Uncomplicated Malaria cases (UM)
- 34 people considered as Control Patients (CP) because they were free from malaria infection (Table 1).

Table 1. General characteristics of the patient cohorts.

Characteristics	Cerebral malaria			Uncomplicated malaria	Control Patients
	Survivors	Deceased	Total		
Patients (n)	27	9	36	37	34
Sex-ratio (M/F)	19/8	8/1	27/9	22/15	20/14
Age Mean (year)	37 (15 - 80)	32 (15 - 66)	36 (15 - 80)	27 (15 - 74)	32 (23 – 61)
Length of Hosp. stay (days)	9 (4 - 39)	4 (1 - 15)	8 (1 - 39)	-	-

n = count; M = male; F = female; d = days.

Demographic characteristics showed a predominance of male patients across all groups. The mean age was approximately 30 years, with a range of 15 to 80 years. Among CM patients, the length of hospital stay varied from 1 to 39 days, with an average duration that differed according to clinical outcome (9 days for survivors and 4 days for those who died). No statistically significant association was found between age, sex, clinical malaria form, or length of hospital stay.

Regarding clinical and biological parameters, patients were classified according to the clinical presentation of malaria. Parasitemia level in CM patients was significantly higher in patients with CM compared to those with UM (30,814.1 ± 14,605.8 vs. 4812.6 ± 1452.7 trophozoites/μL) (Table 2).

In the hematological analysis, leukocyte count and polymorphonuclear neutrophil (PMN) levels were significantly elevated in CM patients compared to UM

patients. Conversely, red blood cell count and hemoglobin levels were significantly lower in the CM group than in the UM group (Table 2). Finally, platelet counts exhibited a progressive decrease with clinical severity, being significantly lower in UM compared to CP, and further decreased in CM compared to UM patients (Table 2).

Table 2. Clinical and biological characteristics of the patient cohorts at the day of admission.

	Cerebral Malaria	*p*	Uncomplicated Malaria	*p*	Control Patients
Blood parasite count (tr/µL)	30814.1 ± 14605.8	<0.001	4812.6 ± 1452.7	-	0
White blood cells (G/L)	10.29 ± 0.92	0.031	6.74 ± 0.76	-	5.58 ± 0.29
Red blood cells (T/L)	3.03 ± 0.24	0.017	4.59 ± 0.15	-	5.03 ± 0.08
Haemoglobin level (g/dL)	10.13 ± 2.52	0.004	13.23 ± 1.66	-	13.90 ± 1.19
Polymorphonuclear neutrophils (G/L)	9.09 ± 1.61	0.028	4.58 ± 1.33	0.036	2.54 ± 1.70
Platelets (G/L)	108.2 ± 99.68	0.003	182.0 ± 67.32	0.001	258.0 ± 50.23

Data are expressed as Mean ± SD; Exact *p*-values indicate comparisons between CM vs. UM (first *p* column) and UM vs. CP (second *p* column); Abbreviations: CM = Cerebral Malaria; UM = Uncomplicated Malaria; CP = Control Patients.

With regard to PMN, their relative proportions differed markedly across groups: they accounted for 60.1% of circulating leukocytes in UM patients, 42.7% in CP, and only 10.3% in those with CM patients. This significantly reduced proportion of neutrophils in CM contrasts with the overall White Blood Cells (WBC) observed in these patients, which remained higher than in UM patients and in healthy controls.

3.2. Plasma Anti-*Plasmodium* IgE Antibody Levels between Clinical Malaria Groups

Assessment of specific plasma IgE levels revealed distinct profiles according to malaria severity. Plasma anti-MSP4-p20 IgE levels were significantly higher in CM patients (median = 1.10 [IQR = 0.20]) compared to UM patients (median = 0.96 [IQR = 0.08]) (Mann-Whitney $U = 173.5$, $p = 0.014$). Similarly, plasma anti-MSP1-p19 IgE levels showed higher median values in CM cases (median = 1.86 [IQR = 1.15]) than in UM cases (median = 1.22 [IQR = 0.24]), representing a strong trend toward elevation in severe cases, although it did not reach formal statistical significance (Mann-Whitney $U = 157.0$, $p = 0.070$).

3.3. Variations in Polymorphonuclear Neutrophils-FcƐRI Positive Events Frequencies According to Severity

At the time of admission in ICU (DoA), we noted a high level of FcƐRI receptors on the surface of polymorphonuclear neutrophils (PMN-FcƐRI) in patients with CM (N = 36, including 27 survivors and 9 fatal cases). Comparison of these PMN-FcƐRI levels between patients suffering from UM (N = 37) and those with CM showed a statistically significant difference with stronger expression in cerebral forms ($p = 0.017$). However, at discharge from the ICU (DoD), the opposite was

noted, *i.e.* a sharp decrease in the PMN-FcƐRI rate in patients with CM, follow-up was performed in surviving CM patients (N = 27; no discharge sample could be obtained for the 9 fatal cases) whereas there was a clear increase in these receptors in patients with UM patients. This latter variation was not statistically significant (Figure 2).

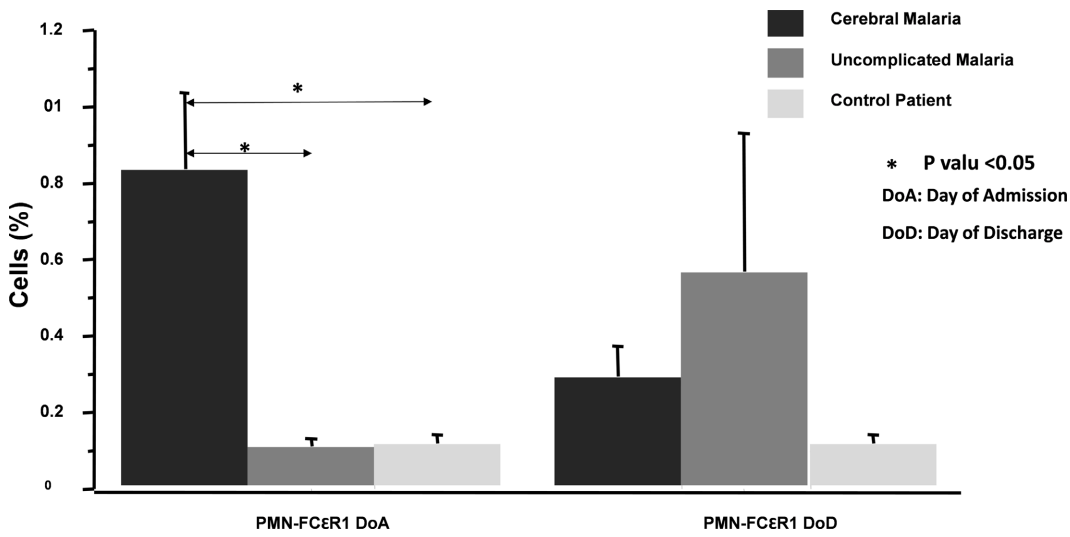


Figure 2. Comparison of polymorphonuclear neutrophils-FcƐRI receptors expression (PMN-FceRI positive events/all PMN events) (%) according to malaria form. DoA: Day of Admission to intensive care unit/DoD: Day of Discharge from ICU. Uncomplicated Malaria (UM): N = 37 at DoA and DoD, Cerebral Malaria (CM) at Admission (DoA): N = 36 total (27 survivors, 9 fatal cases). Cerebral Malaria (CM) at Discharge (DoD): N = 27 (surviving cases only).

3.4. Comparison of Polymorphonuclear Neutrophils-IgE Positive Events Frequencies Based on Severity

The word At DoA, the level of IgE detected on the surface of neutrophils (PMN-IgE) was higher in CM than in UM. The gap narrowed at the discharge assessment; nevertheless, we observe a slightly elevated PMN-IgE level in cases of CM. (Figure 3). However, it should be noted that none of these variations were statistically significant.

3.5. Comparison of Polymorphonuclear Neutrophils-FcƐRI and Polymorphonuclear Neutrophils-IgE According to the Outcome of Cerebral Malaria

The frequencies of positive PMN-FcƐRI and PMN-IgE events at DoA appear to be discriminating the outcome in patients suffering from CM. Indeed, in deceased patients with CM, higher levels of PMN-FcƐRI and PMN-IgE were found compared to patients that survived ($p < 0.001$). This analysis is illustrated in Figure 4(a) and Figure 4(b).

Among survivors, a significant decrease in the PMN-Fc*ε*RI/IgE levels studied was observed between the day of admission (DoA) and discharge (DoD) from the ICU (Figure 5).

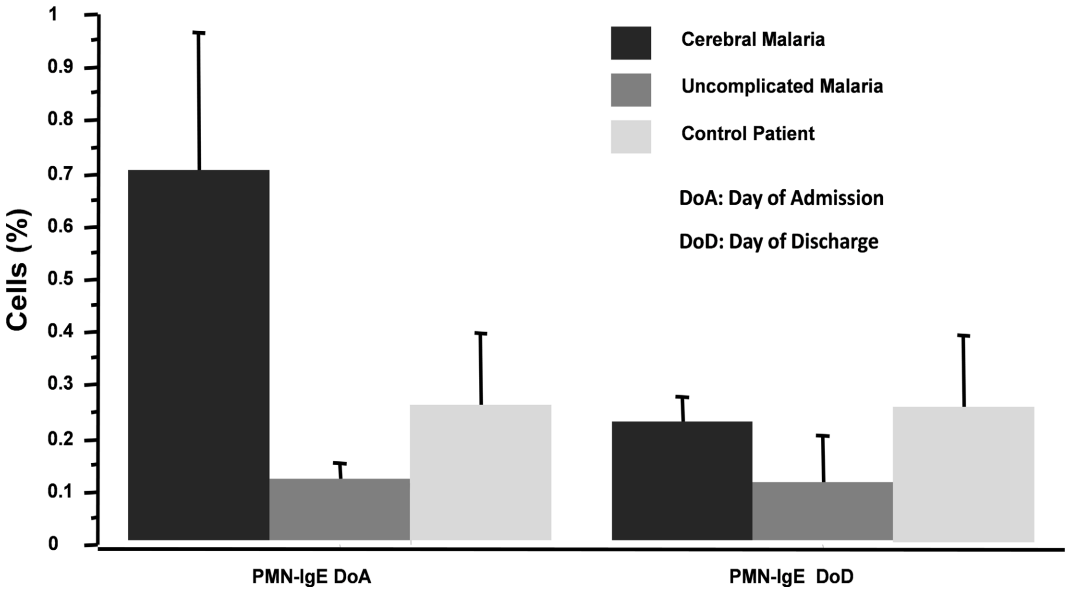


Figure 3. Comparison of surface-bound IgE (Polymorphonuclear neutrophile-IgE positive events/ all PMN events) (%) distributed according to malaria form. PMN-IgE = Polymorphonuclear neutrophile-IgE; DoA = Day of Admission; DoD = Day of Discharge.

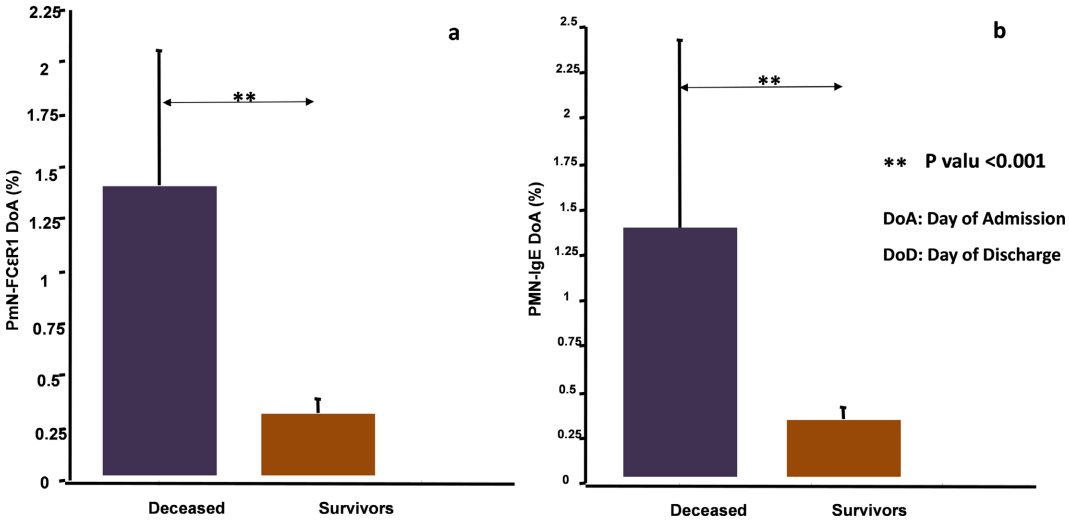


Figure 4. Comparison of polymorphonuclear neutrophils-FcƐRI (a) and polymorphonuclear neutrophils-IgE (b) positive events fequencies (%) according to the outcome of cerebral malaria.

3.6. Analysis of Correlations between PMN-FcƐRI and PMN-IgE Positive Events Fequencies among Cerebral Malaria Patients and between Plasma IgE and PMN-IgE

Results show that overall, we found a positive correlation between PMN-FcεRI levels and PMN-IgE levels ($rho = 0.29$; $p = 0.041$) (**Figure 6**). Furthermore, a correlation was also observed between the PMN-IgE positive events and plasma IgE levels targeted against MSP-4p20 ($p = 0.001$; $Rho = 0.374$). However, we found no correlation between PMN-IgE and plasma anti-MSP1-19 IgE. Nor did we find any correlation between PMN-FcεRI and plasma IgE.

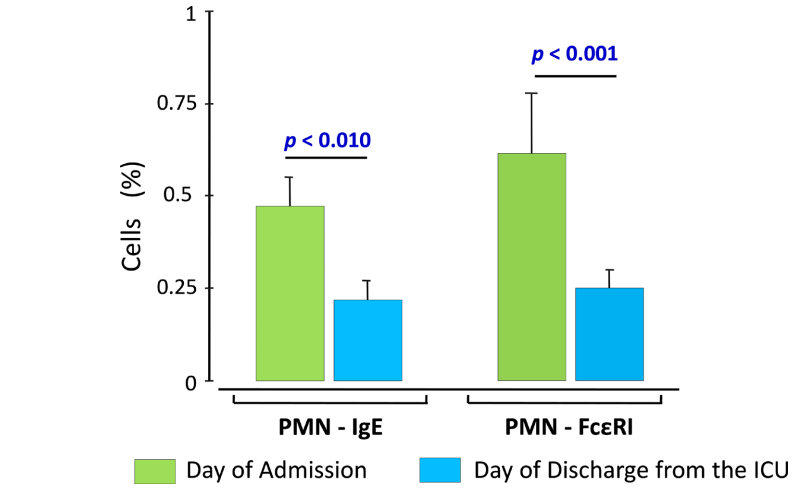


Figure 5. Comparison of PMN-FcεRI and PMN-IgE levels (%) in survivors of cerebral cases at admission and discharge.

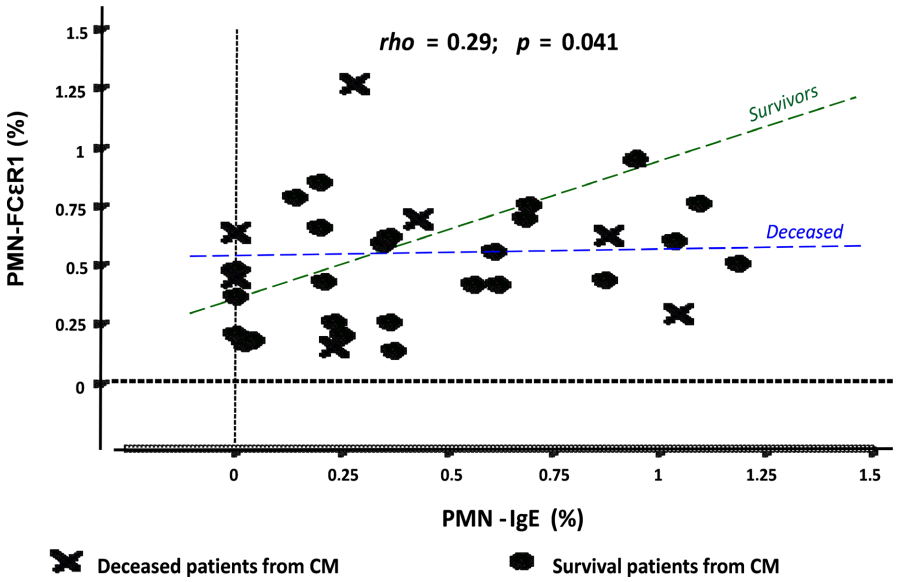


Figure 6. Correlations between PMN-FcεRI and PMN-IgE levels in cerebral malaria cases.

4. Discussion

In the present study, plasma levels of anti-MSP4-p20 IgE antibodies were significantly elevated in patients with CM compared to those with UM, while anti-MSP1-p19 IgE displayed a strong upward trend. These findings align with previous studies showing that high titers of parasite-specific IgE are a distinctive hallmark of severe malaria [3] [20], contrasting with classic effector responses where specific IgE was associated with UM cases and parasite clearance [21]. Mechanistic models of experimental CM have revealed a distinct inflammatory pathway centered on polymorphonuclear neutrophils (PMNs) rather than mast cells or basophils [22]. Indeed, *Plasmodium* infection specifically induces FcεRI expression on circulating PMNs, where surface-bound IgE engagement triggers acute inflammatory responses, vascular hyperpermeability, and microvascular sequestration

[23].

In our clinical cohort, we observed a significantly higher proportion of FcεRI-expressing neutrophils (PMN-FcεRI) at admission (DoA) in patients with CM compared to those with UM. Furthermore, markedly elevated levels of both PMN-FcεRI and PMN-bound IgE were found in fatal CM cases compared to survivors, highlighting their potential role as markers of disease severity and adverse outcome. These human data align with experimental findings by Porcherie *et al.* [8], who identified neutrophil FcεRI as a key contributor to neuro-inflammation and severe pathogenesis. At discharge (DoD), PMN-FcεRI levels markedly declined in CM survivors. While the reduced sample size at discharge represents a limitation of our analysis, the overall kinetic trend suggests that neutrophil FcεRI upregulation is an acute-phase phenomenon associated with severe malarial pathology.

Globally, we observed no overall correlation between PMN-FcεRI or PMN-bound IgE expression and systemic plasma IgE titers, with the single exception of a positive correlation between PMN-IgE and anti-MSP4-p20 plasma IgE. Our general observation that surface IgE on neutrophils does not tightly mirror total circulating IgE aligns with findings by Mora *et al.* [9] in allergic asthma, where neutrophil-bound surface IgE detection was shown to be largely uncoupled from plasma IgE levels. However, in the context of acute *P. falciparum* infection, the specific association observed with anti-MSP4-p20 IgE suggests that local or antigen-specific IgE binding dynamics during high parasitemia warrant further investigation. The lack of broader correlations across other antibody specifications may also reflect sample size limitations during subgroup stratification, highlighting the need for larger prospective cohorts.

Taken together, all these data suggest that elevated circulating anti-parasite IgE actively occupies inducible FcεRI on the neutrophil surface, establishing this specific IgE-neutrophil interaction as a potential key determinant of acute microvascular activation and tissue pathology in human CM.

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Author Contributions

Conceptualization, B.M. and A.D.; methodology, B.M., M.S.N. and C.D.F.; software, B.M.; validation, B.M., A.D., and M.M.; formal analysis, C.D.F.; investigation, B.M. and C.D.F.; resources, B.M.; data curation, B.M. and C.D.F.; writing—original draft preparation, C.D.F.; writing—review and editing, C.D.F. and B,M.; visualization, C.D.F.; supervision, B.M.; project administration, B.M.; funding acquisition, B.M. All authors have read and agreed to the published version of the

manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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