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Review article

COMPLIMENT RECEPTOR TYPE - 1 (CD35) GENE POLYMORPHISM AND *PLASMODIUM FALCIPERUM* MALERIA

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ABSTRACT:

Malaria is a most causative agent for worldwide death. *Plasmodium falciperum* infected malaria most dangerous than other plasmodium species. It has closely association to compliment receptor type -1 (CD35) gene polymorphism. CD35 (CR1) is a cell surface receptor for *plasmodium falciperum* containing PfEMP-1 as a legend. Density of CD35 on erythrocyte can be determined by CR1 allele (HH, HL, and LL). HH allele of CR1 gene express high density of CD35 whereas LL in low density. High density of CD35 is more susceptible to *falciperum* infection. CD35 is also responsible for sever malaria. During plasmodium infection, pro-inflammatory cytokine like TNF-α, IFN-γ levels are increased. The elevated ratio of TNF-α/IL10 indicates *falciperum* infection. Cell adhesion protein like VCAM, ICAM also mediate the malarial infection.

Keyword: *Plasmodium falciperum*, CD35, CR1 allele, TNF-α, IL10, ICAM.

INTRODUCTION:

Malaria is the most infectious and dangerous disease in the world. The World Health Organization (WHO) estimated 225 million malaria cases worldwide with 781,000 deaths due to *Plasmodium* infection per year. Four types of *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*) are responsible for almost all human infections. *Plasmodium falciparum* malaria is responsible for more than one million deaths that occur each year from malaria infection in Africa. Most of these deaths occur as a result of complications such as severe malaria associated anaemia (SMA) and cerebral malaria (CM) [1].

Compliment Receptor 1 (CR1), a protein on RBC cells that having role in immune complex clearance. It's also known as C3b/C4b receptor or CD35. In humans this protein is encoded by CR1 gene is located at on the long arm of chromosome 1 at band 32 (1q32) and lies within a complex of immunoregulatory genes. The Compliment Receptor 1 (CR1) gene polymorphism conform density of CD35 on RBC cells. The human CR1 binds to a major malarial adhesion, the *P. falciparum* erythrocyte membrane protein-one (PfEMP-1). High density of CR1 on erythrocyte indicates high risk of *falciparum* infection [2- 5].

PREVALENCE AND EPIDEMIOLOGY OF *P. FALCIPARUM*: Malaria affects the 300-500 million people each year in which 1-3 million people leading cause of death worldwide annually. There are five *Plasmodium* species that infect humans; *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. These species differ in their morphology, immunology, and geographic distribution. Among the five species that cause malaria in humans, *Plasmodium falciparum* (*P. falciparum*) is the most

virulent resulting in the greatest number of complications and the great majority of malaria-related deaths in children under the age of five. The evolutionary history and geographical distribution of *P. falciparum* reflects a three-way interaction between the parasite, the host, and the *Anopheles* sp. mosquito (the vector for transmission). Circa, 1900 prior to the widespread use of anti-malarials, the distribution of malaria reached the geographic latitudes of 64º north and 32º south [6-7].

However, genetic history and the co-evolution of *P. falciparum* with humans suggest this has not always been the geographic model. The closest relative to the modern day *P. falciparum* is the chimpanzee malaria parasite, *Plasmodium reichenowi*. It has been argued that *P. falciparum* is of African origin because *P. reichenowi* is a parasite that infects African chimpanzees. Despite some controversy, it is generally accepted that the divergence of these two species of malaria occurred approximately 9-10 million years ago, prior to the divergence of humans from non-human primate relatives such as the chimpanzees. It is believed that the major spread of *P. falciparum* in Africa occurred during the "Agrarian Revolution" (4000-5000 years ago) when small nomadic groups began to establish larger settled communities; this lifestyle change provided ideal conditions for sustained *P. falciparum* transmission [8-9].

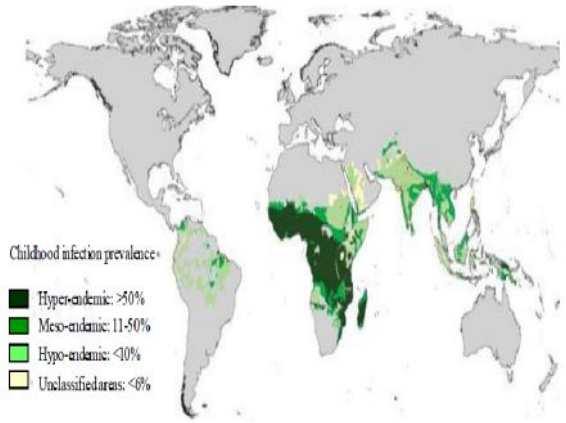


Fig 1: Geographic distribution of *Plasmodium falciparum* malaria [6].

Life cycle of *Plasmodium falciparum* malaria: The *P. falciparum* infection begins when a human host is bitten by an infected female *Anopheles* mosquito, and the mosquito injects sporozoites into the subcutaneous tissue of the human host. The sporozoites, within one hour reach to the liver and infect hepatocytes. The duration of the asymptomatic liver (exo-erythrocytic cycle) stage of the infection is approximately one-two weeks. During this stage, each sporozoite may yield thousands of merozoites [10].

Invasion: The hepatocytes rupture releasing the merozoites into the blood stream (the beginning of clinical disease) where they are able to enter into RBCs by a complex invasion process comprised of four phases: (a) initial recognition and reversible attachment of the merozoite to the RBC membrane. (b) Reorientation. (c) Invagination of the RBC membrane around the merozoite. (d) Resealing of the RBC membrane after completion of merozoite invasion. RBC invasion is a rapid process that is governed by molecular interactions between the merozoites and the host cell surface [11-12].

Primary contact is initiated by a surface coat of proteins that is largely comprised of glycosylphosphatidylinositol (GPI)-anchored membrane proteins. There are at least nine recognized GPI anchored proteins that are predicted to be potential RBC ligands. Merozoite surface protein-1 (MSP-1) is the dominant antigen and is essential for parasite survival. MSP-1 is involved in the initial recognition of the RBC via sialic acid residues found on the RBC membrane. Other important proteins are MSP-2, -3 and -4. *P. falciparum* apical membrane antigen-1 (PfAMA-1) is also essential for successful invasion as it is translocated to the merozoites surface before invasion of the RBCs, and is also present on the sporozoite for invasion into hepatocytes [13-14].

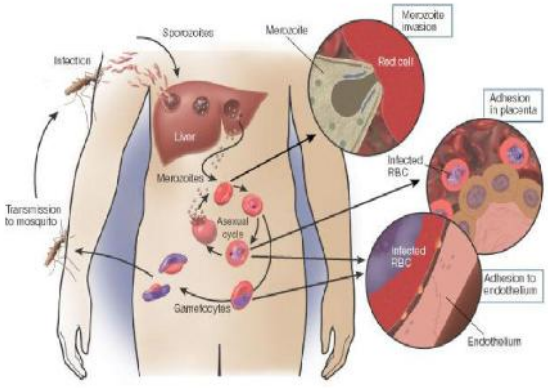


Fig 2: Life cycle of *Plasmodium falciparum* malaria [11].

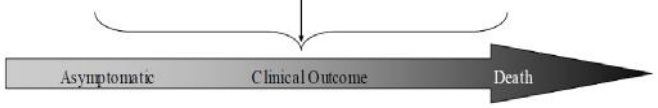
Maturation : Initially, the merozoites develop into an early trophozoite stage known as the "ring form". The ring form persists for 24 hours and matures inside the RBC through a highly active

metabolic state. The *P. falciparum* ring feeds from the host cytoplasm, importing glucose and breaking down hemoglobin into constituent amino acids. Following the ring stage, *P. falciparum* matures and develops to a late stage trophozite. The mature trophozoite stage parasite replicates by nuclear division resulting in schizont stage parasites. Each schizont is comprised of 20-24 merozoites, which are released upon rupture of the infected RBC. When the infected RBCs rupture, merozoites and parasite metabolic waste products such as hemozoin, degradation of hemoglobin, and parasite toxins are released. The majority of the merozoites will invade other RBCs continuing the asexual cycle; however, some parasites will form sexual stage forms called gametocytes which are then transmitted to new hosts by the *Anopheles* vector [11-17].

Pathophysiology of *Plasmodium falciparum* malaria: Infection with *P. falciparum* results in considerable morbidity and without treatment may be fatal. The clinical outcome of malaria depends on many contributing factors including the parasite's virulence, the host's response, geographical, and socio-economic factors (Table 1).

Table 1. Factors contributing to the clinical outcome of *P. falciparum* infection [11].

Parasite Factors	Host Factors	Geographic and Social factors
-Drug Resistance -Multiplication rate -Invasion Pathways -Cytoadherence -Rosetting -Malaria toxins (hemozoin) -Antigenic Variation (PfEMP1)	Immunity Genetics: Sickle cell, thalassaemia, ABO blood type Age Pregnancy Proinflammatory cytokines	-Transmission intensity -Culture and economic factors -Access to treatment



The combination of these factors result in a range of possible outcomes for the host, including asymptomatic infection, uncomplicated malaria infection, severe infection (severe malaria anemia and cerebral malaria) and death.

Clinical stages of malaria pathogenesis: There are three defined clinical stages of malaria pathogenesis: uncomplicated malaria, severe malaria, and cerebral malaria. Uncomplicated malaria initially presents with fever and chills, nausea and headache, sometimes associated with diarrhea and vomiting. Unfortunately, because of the similarity in symptoms, malarial infection is often mistaken for many other infections including influenza or gastro-intestinal infection and is therefore not properly treated [18]. In 1990, the World Health Organization (WHO) established criteria for the diagnosis of severe malaria. The major criteria include neurological involvement (cerebral malaria), pulmonary edema, acute renal failure, and severe anemia. Severe anemia is the second most common symptom of *P. falciparum* infection and is caused by the destruction of RBCs and overall decreased erythropoiesis. Acidosis and hypoglycemia are the most common metabolic complications [4,19].

Cerebral malaria is the most common cause of death in adults and children with severe malaria. According to the WHO, the strict definition of cerebral malaria requires the presence of *P. falciparum* parasitemia and unarousable coma with a Glasgow Coma score of 9 or less; all other causes of coma, such as hypoglycemia, bacterial meningitis and viral encephalitis, need to be excluded. Typical neurological symptoms include coma, seizures, edema, and brainstem damage. Engorgement of cerebral capillaries and venules filled with infected RBCs and non-infected RBCs are typical histopathological findings in cerebral malaria. As the infection progresses, the increasingly detrimental pathogenesis of *P. falciparum* malaria is believed to be caused by two main factors: (a) an imbalance of cytokine production; and (b) the sequestration of infected RBCs in the microvasculature of vital organs [20-21].

Inflammatory response:

P. falciparum infection results in an increase of both pro-inflammatory cytokines and anti-inflammatory cytokines. However, in cerebral malaria, there is an unbalanced and excessive production of the pro-inflammatory response. Blood concentrations of pro-inflammatory cytokines, especially tumor necrosis factor (TNF), interferon gamma (IFN-γ), and IL-6, have been shown to be raised in cerebral malaria. TNF may contribute to malaria pathogenesis including cerebral malaria. TNF up regulates endothelial cytoadherence receptors such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-

selectin. TNF may cause hypoglycemia and dyserthryopoesis, and has been shown to induce the release of nitric oxide (NO) which interferes with synaptic transmission [22-23].

Parasite sequestration:

P. falciparum has a unique ability to adhere to host microvasculature endothelium, a process known as sequestration. Sequestration causes microvascular obstruction and compromises the blood flow through tissues such as the liver, spleen, lung, and brain. The effects of sequestration include mechanical obstruction (which can lead to hypoxia), metabolic disturbances and is a central point where parasite toxins and inflammatory mediators concentrate [24].

Increased expression of cytoadherence receptors enhances infected RBC sequestration to the endothelium via parasite derived proteins (expressed on the surface of the infected RBC), such as PfEMP-1. The principal parasite surface protein and sequestration ligand known as *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1), encoded by var genes, is expressed. It is predominantly mature stage parasites (trophozoites and schizonts) that adhere to the microvasculature [25].

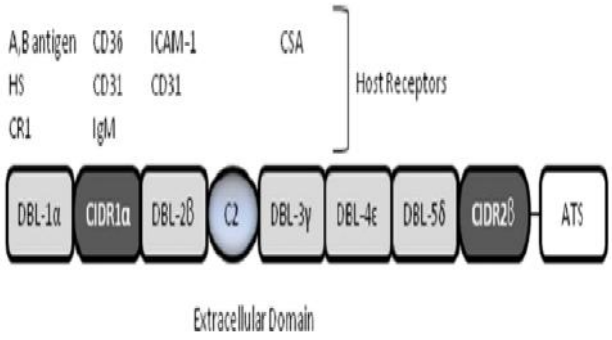


Fig 3: The PfEMP-1 molecule and associated host receptors [26].

The PfEMP-1 molecule has a pivotal role in the pathogenesis of *P. falciparum* as a number of host receptors are recognized by the various extracellular binding domains of PfEMP-1. Thus, permitting the infected RBCs to adhere to host endothelium. In the case of cerebral malaria, PfEMP-1 may mediate adhesion to several adhesion molecules, in particular ICAM-1 which is unregulated on the cerebral vascular endothelium [26].

Innate immunity to *P. falciparum* malaria:

The innate immune response is crucial to the outcome during a *P .falciparum* infection. Innate immune responses take effect immediately and provide an early defence until the adaptive immune response is engaged. In some cases, an infection by *P. falciparum* may be controlled by the innate immune system. 61 Parasite burdens observed in non-immune individuals with acute *P. falciparum* malaria are lower than expected based on parasite replication rates observed *in vitro*, suggesting that the innate immune system can contribute to effective control of acute parasite replication before the adaptive immune response develops [27].

The innate immune system functions to limit the maximum parasite density, but gradually acquired adaptive mechanisms complete parasite elimination. The innate immune system is essential for most inflammatory responses that are triggered by monocytic cells, other leukocytes and mast cells through their innate sensing receptors. Macrophages are important in innate immunity as they are able to clear parasitized RBCs in the absence of opsonizing malaria-specific antibodies. It is hypothesized that there are two methods of infected RBC uptake by macrophages. The predominant method of uptake involves the binding of non-specific IgG and complement to the surface of infected RBCs, and increased exposure of senescent RBC markers such as exposure of phosphatidylserine (PS). This method induces the release of pro-inflammatory cytokines. The second method of uptake is CD36 mediated, which involves the binding of CD36 on the macrophage to PfEMP-1 on the infected RBCs. This method does not involve the release of pro-inflammatory cytokines [28-29].

There are three main biochemical pathways that result in activation of the complement system: the classical complement binding pathway; the mannose-binding lectin pathway; and the alternative pathway. All three lead to the formation of C3 and C5 convertase which results in the cleavage of C3 and C5 into C3a, C3b, C5a and C5b, respectively. RBCs opsonized by IgG and complement (C3b) are recognized by the Fc receptor (FcR) and CR1 (respectively), and phagocytosed by macrophages.This method of clearance is effective in senescent and damaged RBCs, and also in *P. falciparum* infected RBCs [30].

COMPLEMENT RECEPTOR 1(CD35):

CR1 is a 200-kDa single chain membrane bound glycoprotein and a member of the regulators of

complement activation (RCA) gene cluster. CR1 possesses complex tri and tetra N-linked oligosaccharides in its mature form and the gene for this protein is located on the q32 arm of chromosome 1. It is composed of a number of repeated domains called short consensus repeats (SCRs) each of which is composed of 60 amino acids containing four invariant cysteines. The extracellular domain of the CR1 is composed of 30 SCRs, the first 28 of which are arranged in tandem repeats in homologous groups of 7, with each group known as long homologous repeat (LHR). SCRs 8-12 and SCRs 15-18 preferentially bind to C3b and SCRs 1-4 preferentially bind to C4b. The region of CR1 that interacts with infected erythrocytes to form rosettes has been mapped to LHRB and first three SCRs of LHR-C, SCR 10 and 17 have been particularly found to play an important role in this interaction [31-32].

Effect of differential CR1 expression on malarial pathogenesis; Differences in the expression of CR1 on erythrocytes might determine susceptibility of an individual towards development of cerebral malaria and severe malaria-associated anemia. In one of the studies it was suggested that young children may be more susceptible to SMA because of their lower levels of RBC complement regulatory proteins, which make them less equipped to handle IC formation and complement activation. Previously same group of researchers had proved that a decline in levels of CR1 and increase in immune complex levels significantly associates with SMA. The mechanism for the loss of CR1 from the surface of erythrocytes is being investigated. A series of experiments indicated that CR1 present in the form of clusters on RBC surface undergoes unclustering due to the binding of IgM - C3b complexes to glycophorin A. Unclustering might promote rapid loss of CR1 from the surface of erythrocytes infected with the malaria parasite [33].

CR1 polymorphisms; CR1 is a highly polymorphic glycoprotein. Three different polymorphic forms of CR1 have been identified, namely structural (size variation 160-250 kDa), density (high and low expression on RBCs controlled by alleles H and L) and knops blood group (McC (a^+)/McC (b^+); Sl (a^+)/Sl (a^-); Kna/ Knb).

***a) Structural polymorphism*:**

Four different structural polymorphic forms of CR1 are known, namely A, B, C and D (CR1*1, CR1*2, CR1*3, CR1*4) with respective molecular weights of 190, 220, 160 and 250 kDa (under non-reducing conditions). This polymorphism is regulated by four autosomal co-dominant alleles. A polymorphism in the CR1 transcripts with incremental differences of 1.4 kb in mRNA was present in donors expressing the various polymorphic forms. This difference corresponds to the size of one LHR and 40 kDa difference, seen among allotypic forms of CR1. Therefore on the basis of this observation it was suggested that the insertion or deletion forms the basis of structural polymorphism. Analysis of restriction fragment length polymorphism (RFLP) suggested that intragenic duplication rather than alternate mRNA splicing is responsible for the allotypic differences [34-35].

b) Density polymorphism:

Second type of polymorphism is a Hind III RFLP, which in Caucasians but not in Africans,

correlates with CR1 copy number on erythrocytes. Homozygotes for the L (low expression) allele usually express fewer than 200 copies of CR1, homozygotes for the H (high expression) allele express several times this number and heterozygotes are intermediate. This polymorphism arises due to a single base change in the intron of d1d2 segment within the LHR-D (Long homologous repeat) region resulting in the generation of a polymorphic Hind III site within this region [36].

Genotypic frequencies of HH, HL and LL forms have also been studied in the malaria endemic and non-endemic groups in different populations. In nonendemic Caucasian and Choctaw population groups in USA, the gene frequencies for H and L alleles were found to be 0.82, 0.18 and 0.84, 0.16 respectively. In endemic Black Africans the gene frequencies for H and L alleles were 0.85 and 0.15; in S. Chinese-Taiwanese 0.71 and 0.29; in Pacifi c Asians 0.42 and 0.58 and in Cambodians 0.53 and 0.47 respectively [37].

c) Knops polymorphism:

The third type of polymorphism represented by Knops blood group system is of particular interest. In this system, Mca and Mcb is one allelic antigen pair and Sla and Vil is another pair. The corresponding phenotypes for the fi rst pair are McC (a^+) and McC (b^+) and for the second pair are Sl (a^+) and Sl (a^-). Studies have now established the molecular basis for Knops polymorphism. These antigens have been localized on the LHR-D segment of CR1. Single

nucleotide polymorphisms occurring in SCR 25, which lead to amino acid substitutions, result in generation of these polymorphic forms Population based studies have been carried out to determine the distribution of different types of Knops polymorphic forms in different populations. The gene frequencies for Sl (a^+) and Sl (a^-) in African American persons are almost equal (0.48 vs. 0.52) wheras Sl (a^-) is greatly increased in Africa [38-39].

Out of the three polymorphic forms, size polymorphism has not been found to play a role in determining susceptibility to severe malaria. With regard to density polymorphism, some studies suggest that low-density allele confers protection against malaria, whereas another suggested that low-density allele might be a risk factor for severe forms of malaria. Erythrocytes with low CR1 expression (because of the homozygous LL genotype of CR1) have been shown to form reduced number of rosettes with *Plasmodium falciparum* infected cells [40-42].

CYTOKINES AND MALARIAL INFECTION:

The study of immune response against *Plasmodium* is based on murine experimental systems. Both cell mediated and antibody-dependent immunity is required for adequate protection against malarial infection in different mechanisms. In addition, innate immunity is thought to play a crucial role in clearing *Plasmodium* from parasitized hosts [43]. In splenic response, tissular changes that provoke alterations in blood flow through the organ. These changes prevent the access of infected erythrocytes to splenic tissues in which the immune response is going on until armed effector cells are produced. In general, most of the evidence supports the hypothesis that cells from the monocyte-macrophage lineage are more effective than neutrophils at phagocytosing parasitized erythrocytes [44].

P. chabaudi infection in γ/δ T-cell-deficient mice has exacerbated early and chronic parasitemias. Resulting early production of gamma interferon (IFN-γ) and tumor necrosis factor alpha (TNF-α) both to spleenic γ/δ T lymphocytes and to natural killer (NK) cells [45-46].

Both the cellular and humoral responses are pivotal elements in the eradication of *Plasmodium* from the body, and both are critically dependent on γ/δ $CD4^+$ lymphocytes. It has been firmly established that $CD4^+$ T cells are comprised of at least two functionally different subsets, distinguished on the basis of lymphokine secretion in Th1 (IFN-γ-producing) and Th2 (interleukin-4 [IL-4]/IL-5-producing) cells. $CD4^+$ T cells of either Th1 or Th2 type also have regulatory functions in human *P. falciparum* malaria. Both Th1 and Th2 responses seem to be required to control the infection, but they need to be adequately tuned in intensity and time [47-48].

Cytokines in Early Protection; The early production of IFN-γ is responsible for resistance against infection. In support of this point, analysis of IFN-γ $R^{-/-}$ mice infected with *P. chabaudi chabaudi* showes a critical role of IFN-γ in immunity against this pathogen. Interestingly, *Tan et. al.*[50] reported that IFN responsive factor $(IRF\text{-}1)^{-/-}$ mice infected with *P. berghei* revealed that lower mortality than wild-type mice, although they produced no IFN-γ or NO [51-53]. There are mechanisms of resistance independent for IFN- γ and NO. In which treatment in vivo with anti-IFN-γ exacerbates *P. yoelii* 17XL infection in C57BL/6 because mice treated with antibody die earlier. In contrast, treatment with aminoguanidine, an irreversible inhibitor of NO production, has no effect. Consistently, mice lacking inducible nitric oxide synthase ($iNOS^{-/-}$) cleared *P. berghei* XAT (an attenuated variant of *P. berghei* NK65) as effectively as did wild-type animals. In this case, resistance was dependent on IFN- γ, since it's in vivo, blocking provoked progression of parasitemia and death [54].

The overall conclusion that can be drawn from this is that the role of a particular cytokine is likely to be different at different stages of the infectious process. A prominent role in switching from Th1 to Th2 responses is attributed to IL-10. Therefore, it is probably involved in controlling the adequate timing of antiparasitic responses. Early IL-10 production has been associated with susceptibility to infection, and it is thought that this cytokine has a prominent anti-inflammatory effect, limiting in some way the damage inflicted on normal tissues by an excessive Th1 response [55-56].

Cytokines in the Immunopathology of Malaria; The pathogenesis of malaria is complex and containing immunologic and non-immunologic mechanisms. In general, it is now accepted that severe malaria is the consequence of alterations in many tissues and organs. These dys-functions often lead to metabolic acidosis and localized ischemia. It is evident that parasite factors can contribute to the severity of disease, as is clear from their ability to

infect a high percentage of erythrocytes or to induce production of proinflammatory cytokines. In particular, much evidence has been accumulated that glycosylphosphatidylinositols from *Plasmodium* as an important pathogenic factors due to their ability to induce TNF-γ and IL-1 [57-58]. This view is strongly supported by the fact that the toxicity of malaria parasite extracts can be neutralized with monoclonal antibodies against this moiety in experimental models [59]. It is noteworthy that recent work suggests that the presence of anti-glycosyl phosphatidyl inositol antibodies in the serum of patients may provide protection against clinical symptoms of malaria. Therefore, cytokines, viewed as potential pathogenic elements, can contribute either directly or indirectly to many pathological processes [60-61].

Cytokines in the Diagnosis of Malaria; The Th2 profiles have been reported in humans, with elevated levels of IgE being found in the blood of malaria patients, presumably due to the predominance of Th2 cells over Th1 helper cells. This polarization was significantly higher in the case of patients suffering from severe malaria [62]. Th1 responses are important for clearance of *P. falciparum* malaria. In non-immune children with severe *P. falciparum* malaria showed lower levels of IL-12 and IFN-γ in serum and had a reduced capacity to produce them after in vitro stimulation. It is interesting that children with severe anemia had the highest levels of TNF-γ [63]. It has been reported that children with prior mild malaria showed an enhanced ability to express iNOS in vitro over children with prior severe malaria. Furthermore, *Luty et. al.* [64] found that peripheral blood mononuclear cells of patients with mild malaria produced IFN-γ in response to malarial antigens, whereas those with severe malaria did not. However, no associations were found with TNF-γ production. The studies on Ghanaian children showed that only patients with uncomplicated malaria had a positive correlation with levels of TNF- α and soluble TNF- α R1 and TNF- α R2 in serum. In the same study, children with CM had high levels of TNF- α, and although TNF- α level were associated with fever no differences were observed in soluble TNF- α receptors. Interestingly, children with fever and detectable parasitemia, but not afebrile parasitized patients, had elevated levels of TNF- α [65]. Patients who died from *P. falciparum* malaria had higher amounts of IL-6, IL-10, and TNF- α in serum than did the patients who survived.

CONCLUSION

Malaria is a worldwide spreaded disease due to plasmodium species (*P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*). It affects 300-500 million people in which 1-3 million going to death. All of plasmodium species, *P. falciparum* is very dangerous leads to cerebral malaria. For completing, his life cycle, plasmodium having two host first mosquito (as a vector) and second human. When plasmodium is introduced in blood by mosquito, it attached with RBCs through CD35 (CR1) which act as a receptor for PfEMP-1 (present in plasmodium) and circulate in blood stream. CD35 is a cell surface receptor and its gene present in chromosome no. 1. It is also known as Complement Receptor Type 1 (CR1). Density of CD35, in cell surface is determined by CR1 gene polymorphism. There are types of CR1 polymorphism (a) Structural polymorphism (b) density polymorphism (c) knops polymorphism. High density of CD35 is more susceptible to plasmodium infection. ICAM-1 and VCAM-1 are also play important role in malarial pathogenesis. Cytokine profiling indicates malarial severity. Pro-inflammatory cytokine TNF-α and INF- γ level is increased during malarial infection where as IL10, IL4, and IL6 are anti-inflammatory cytokine.

Conflict of interest: Nil

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