

Assessment of Cytokines Levels In Malaria And Their Respective Roles In The Pathological Severity

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Abstract:

Cytokines are term used to refer to minor peptides or proteins secreted by the body cells. TNF (TNF- α and TNF- β), IFN (IFN- α , IFN- β and IFN- γ) interleukins IL-1 β , IL-4, IL-6, IL-10, IL-12, IL-18, CCL4/RANTES, and TGF β are among the variety of soluble mediators released by various innate immune cells. TNF- α , IFN- γ , IL-6, IL-8, IL-18, and MCP-1 are examples of pro-inflammatory cytokines that have been linked to severe malaria as well as its fatality. This review is aimed at assessing the levels of cytokines in malaria and their role in the severity of the disease. A total of 21 primary studies were fetched from different databases or repositories; Pubmed, Elsevier and Google scholar. Article used in this study met the following criteria; must be primary studies, in peer reviewed journals, indexed additional with any of the following; Doi, crossref, Scopus, web of science and Directory of Open Access Journals (DOAJ). Artemisinin-based therapy, Artemether-lumefantrine, combination of dihydroartemisinin-piperaquine, and Artemisinin-naphthoquine combination therapy alongside emerging treatments like the use of medicinal plants; *Morinda lucida*, and *Nauclea latifolia*, among others, are also proven effective medications against *Plasmodium parasite*. This research has proven that the levels of IL-6 and IFN- γ in people with symptomatic malaria is high.

1. Introduction

Cytokines according to Zhang and An (2007), is a general term used to refer to minor peptides or proteins secreted by the body cells, which play several roles in the ways cells communicate with each other. Cytokines includes cells made by lymphocytes which are referred to as lymphokines (Brocker et al. 2010), those made by leukocytes known as interleukin (Julius and Roberts, 2009), the monokines secreted by the monocytes, and the chemokines synthesized via chemotactic activities (Raman et al., 2011). Ferreira et al. (2019) reported that cytokines are a cell-signaling category of extracellular polypeptides/glycoproteins with low molecular weight that are generated

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by various immune cells, primarily T cells, neutrophils, and macrophages, and are important for immune response regulation and promotion. In addition to acting on major lymphocyte growth factors and other biological processes, these polypeptides stimulate cells and signaling molecules to go toward wounds, infections, and inflammatory areas (Ferreira et al., 2019). These cells, which are at the forefront of the immune system's defense, prevent the opportunistic invasion of a wide variety of viral, fungal, bacterial, and parasitic pathogens, in part by producing a profusion of cytokines and chemokines that they use to coordinate immune responses with other cells. TNF (TNF- α and TNF- β), IFN (IFN- α , IFN- β and IFN- γ) (Ferreira et al., 2019), interleukins IL-1 β , IL-4, IL-6, IL-10, IL-12, IL-18, CCL4/RANTES, and TGF β are among the variety of soluble mediators released by various innate immune cells (Iwasaki and Medzhitov, 2010; McGettrick and O'Neill, 2007). According to the studies conducted by Akdis et al. (2015) and Sims and Smith (2010), interleukins (ILs) are a category of secreted proteins that have a variety of forms and roles. There are currently 40 interleukins known, some of which are further broken down into subtypes (like IL-1 α , IL-1 β).

The effect of cytokines is seen on the cells from which they are synthesized, surrounding cells, and cells that distant (Zhang and An., 2007). Paige and Jennifer (2011) reported that cytokines play a crucial role in the immune system because they govern the equilibrium across humoral and cell-based immune system responses and also the maturation, development, and responsiveness of certain cell populations. They act through cell surface receptors. The actions of some cytokines can be complicatedly increased or decreased by other cytokines. They are distinct from hormones, significant cell signaling chemicals as well. The host immunological responses to infection, inflammation, trauma, sepsis, cancer, and reproduction depend on cytokines in both health and illness.

With respect to malaria parasite infection and severity, cytokines are essential in controlling the severity of the disease, parasite load, and malarial symptoms (Farrington et al., 2017). TNF- α , IFN- γ , IL-6, IL-8, IL-18, and MCP-1 are examples of pro-inflammatory cytokines that have been linked to severe malaria as well as its fatality (Lyke et al., 2004; Farrington et al., 2017). According to the research outcome conducted by Lyke and colleague (2004), interleukin-6, IL-10, tumor necrosis factor alpha, and IL-12 were found to be considerably greater in serious instances compared to healthy controls. In comparison to subjects with simple malaria, significantly higher levels of IL-6 and IL-10 were found in severe malaria patients. IL-6 and IL-10 levels were considerably higher in cerebral malaria cases than in severe malaria cases without cerebral symptoms. On the other hand, children with severe anemia had lower levels of IL-6 and IL-10. IL-6 levels were considerably lowered in hyperparasitemia (Lyke et al., 2004). These findings highlight the intricate connections between inflammation and illness in malaria, particularly *P. falciparum* infection. This review is aimed at assessing the levels of cytokines in malaria and their role in its severity.

2. Methods

A total of 21 original articles were sourced from different databases for this review study. The repositories or academic databases considered were Pubmed, Elsevier and Google scholar. In addition, the journals on which the articles were published as criteria for inclusion must be peer reviewed journals, indexed additional with any the indexing partners; Doi, Crossref, Scopus, Web of Science, Directory of Open Access Journals. All articles considered were original articles focused on the subject of malaria, cytokines or malaria and cytokines in combination.

2.1. Epidemiology

Study conducted by Hartman et al. (2010) revealed that in Sub-Saharan Africa, maternal malaria is thought to be responsible for about 200,000 estimated child fatalities annually. Around 125 million pregnant women are at vulnerability to the disease each year. In the United States, Taylor et al. (2012) reported that each year there is a record of 1,300 to 1,500 malaria instances, whereas the figure in Western Europe, malaria cases reported stands at about 10, 000 per year. The Centers for Disease Control and Prevention, (CDC) (2018) reported that in 1951, malaria was no longer a significant public health issue in the United States, although there are still instances of occasional local outbreaks. According to Kajfasz (2009), between 1993 and 2003, the disease claimed the lives of almost 900 persons throughout Europe. In recent years, the global cases as well as the fatalities resulting from malaria have decreased. Insecticide-treated bed nets and combination treatments based on artemisinin have been used widely (Howitt et al., 2012), and this has led to a 60% decrease in malaria-related deaths in 2015 compared to an estimate of 985,000 in 2000, according to the WHO and UNICEF (UNICEF, 2015).

Since 2000, initiatives to reduce the disease's prevalence in Africa have had some success, with rates on the continent reportedly declining by 40% (Bhatt et al. 2015). According to the work of Greenwood and Mutabingwa (2002), it was reported that in broad regions, the spatial distribution of malaria is complicated, and locations with and without malaria are frequently found within close proximity to one another. Rainfall, constant elevated temperatures, extreme humidity, stagnant pools where mosquito larvae easily mature, and other factors all contribute to the widespread incidence of malaria in tropical and subtropical areas, giving these areas the conditions they need for ongoing reproduction (*Jamieson et al. 2006*). Based on Abeku (2007)' research, by tracking rainfall, malaria outbreaks have been rather accurately anticipated in drier places. Rural areas witness malaria at a higher degree when compared to the urban regions. For instance, malaria is practically nonexistent in a number of Southeast Asian cities in the Greater Mekong Subregion, yet it is widespread in many rural areas, particularly along international borders and the edges of forests according to Cui et al. (2012); a situation contrary to what is obtainable in the African continent where malaria parasite infection is prevalent in both the urban and rural areas (Machault et al. 2011).

2.2. Pathogenesis

According to the research conducted by Bledsoe (2005), two phases contribute to the development of malaria infection: the exoerythrocytic phase, which occurs in the liver, and the erythrocytic phase, which concerns the red blood cells. *Sporozoites* from an infected mosquito's saliva infiltrate the bloodstream after a blood meal, travel to the liver, and infect hepatocytes. At the liver, they reproduce asexually and asymptotically between 8-30 days. The organisms undergo differentiation to produce hundreds of merozoites after potentially becoming latent in the liver. After the rupture of the host cells, the merozoites escape into the blood and infect red blood cells to start the erythrocytic stage of the life cycle (Bledsoe, 2005). By encasing itself in the host liver cell's contaminated cell membrane, the parasite exits the liver undetected (Vaughan et al. 2008). The parasites continue to develop inside the red blood cells, reproducing once more asexually and periodically erupting from their host cells to infect brand-new red blood cells. This amplification cycles happen multiple times. The simultaneous waves of merozoites fleeing and infecting red blood cells are what lead to the traditional descriptions of waves of fever (Bledsoe, 2005).

Because the parasite spends the majority of its human life cycle inside the liver and blood cells and is largely undetectable to immune surveillance, the parasite is relatively safe from attack by the body's immune system. However, the spleen kills contaminated blood cells that are still in circulation. Infected blood cells with the *P. falciparum* parasite possess adhesive proteins on their surface that cause the blood cells to adhere to the walls of tiny blood capillaries, preventing the parasite from passing through the spleen and the general circulation (Tilley et al., 2011). According to Mens et al. (2010), the microvasculature is blocked, which results in symptoms similar to that found in placental malarial infection. Also, the blood-brain barrier can be breached by trapped red blood cells, leading to cerebral malaria (Rénia et al., 2012).

2.3. Cytokines Involvement in Malaria

According to Katrien et al. (2016), there is a strong immunological inflammatory response to *P. falciparum* infection, and this response is based on the quantity of soluble mediators like cytokines, chemokines, and other inflammatory molecules in the blood. These mediators are crucial at injury sites and also control several cellular functions (Chen et al., 2018). Kumar et al. (2019), cited in his study that for malaria to be resolved, efficient promptly inflammatory cytokines must be counterbalanced by suitable anti-inflammatory cytokines. In malaria, cytokines are essential for controlling the disease's magnitude, parasite burden, and symptomatology (Farrington et al., 2017). Tumor necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ), interleukin (IL-6), IL-8, IL-18, and MCP-1 are examples of pro-inflammatory cytokines that have been linked to deadly malaria (Farrington et al., 2017; Lyke et al., 2004). The regulatory cytokines, on the other hand, are anti-inflammatory cytokines like TGF- and IL-10. They lessen the impact of the inflammatory response (Noone et al., 2013). According to several studies, the ability of the host's body to quickly create

sufficient amounts of pro-inflammatory cytokines is necessary for the successful clearance of malaria infection from the system (Sibhatu et al., 2019).

Based on the study conducted by Chen et al. (2018), disease development is slowed when anti-inflammatory cytokines are effective at controlling pro-inflammatory cytokines. Therefore, an equilibrium of pro-inflammatory and anti-inflammatory cytokines is necessary for an immune response to *P. falciparum* to be successful (Peter et al., 2014).

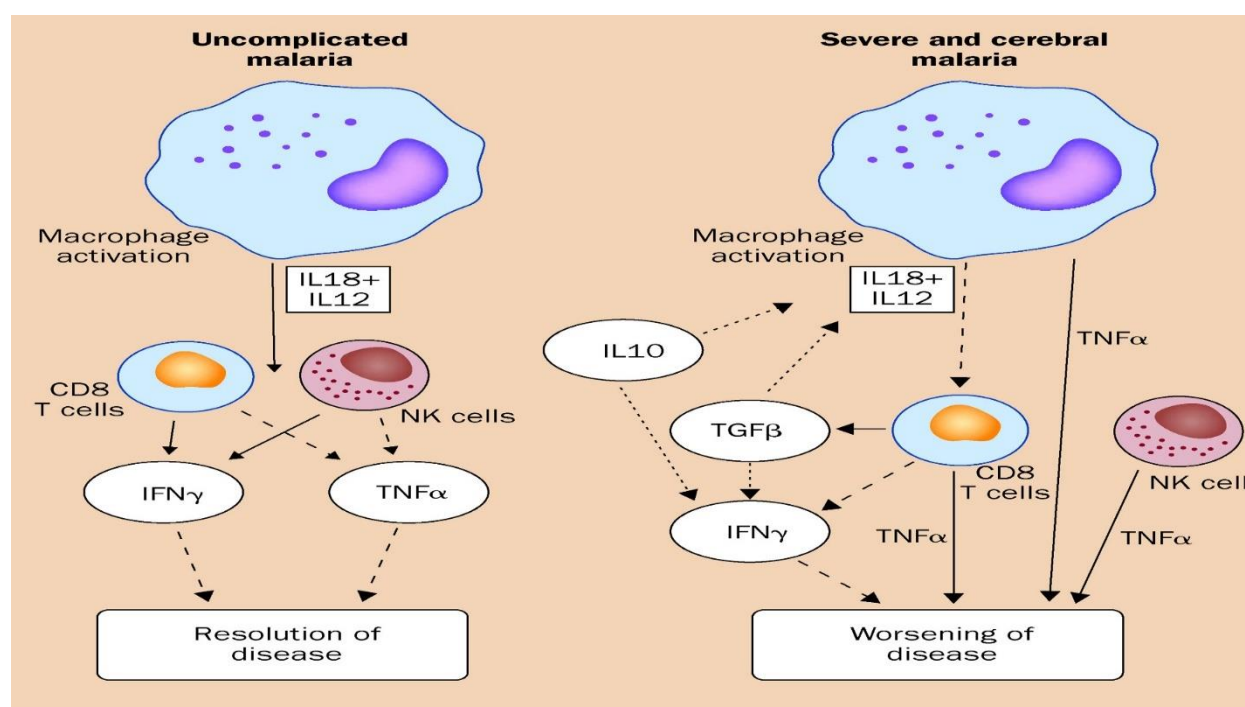


Figure 1: Suggested interactions between IL12 and IL18, pro-inflammatory cytokines, and TGFβ and

IL10, anti-inflammatory cytokines, in simple or severe, complicated malaria. Solid lines denote enhanced production of cytokine, dashed lines represents reduced cytokine production, while dotted lines denote blocked cytokine production. IFN=interferon (Omer et al., 2000).

2.4. Clinical Manifestation of Cytokines in Malaria

Signs and Symptoms

The clinical presentation noted in malaria is due to an imbalance of inflammatory reactions. Leukocyte entrapment in cerebral malaria is the product of elevated levels of cytokines and chemokines (Dunst et al., 2017). According to Oyegue-Liabagui et al. (2023), each time a malaria infection cycle occurs, merozoites are released, causing fever episodes during the erythrocytic phase, which is accompanied by high

temperature, signaling the onset of the clinical signs of the disease. Ansari et al. (2009) reported that hematological factors such red blood cell count, hemoglobin level, and platelet count are impacted by *Plasmodium* infection because it specifically targets and kills red blood cells. Acute *P. falciparum* malaria patients have been reported to have thrombocytopenia. By releasing antigen on their membrane, the parasites also cause the breakdown of healthy red blood cells according to Douki et al. (2003) and Layez et al. (2005). This activity of red blood cell destruction also leads to platelet aggregation (Wassmer et al., 2006).

Based on the study conducted by Oyegue-Liabagui et al. (2023), children who had *P. falciparum* infection symptoms had significantly greater levels of IL-6 and IFN- γ than those who had no symptoms or were not infected. Additionally, children with symptoms and those who were asymptomatic was shown to possess elevated levels of IL-12p70, IL-13, and IL-22 that were considerably greater than those of children who were not affected. IL-10 levels were, however, considerably greater in symptomatic children in comparison to asymptomatic children, who subsequently had considerably greater levels than uninfected children. All of these imply that *P. falciparum* promotes the Th1, Th2, and Th17 cytokines. Additionally, the positive correlations found in the current study between a number of cytokines in both asymptomatic and symptomatic *P. falciparum* infections point to the possibility of contemporaneous production of these cytokines (Oyegue-Liabagui et al., 2023). Bueno et al. (2012) and Keswani et al. (2014) cited in their research that the Th1 and Th17 cytokines activities which are connected to initial immunological mechanisms that regulate *Plasmodium* infection may be involved in the defense mediated by pro-inflammatory response. According to Aubouy et al. (2002), during acute malaria infection, peripheral blood mononuclear cells produce the majority of the IL-6 and they have been revealed to be considerably higher in children with malaria symptoms (Abdullahi et al., 2021).

It has also been shown that *Plasmodium falciparum* infections cause significant amounts of parasite-infected red blood cells, which in persons without malaria, cause widespread inflammation and high temperature (Oyegue-Liabagui et al., 2023). It has also been shown that *Plasmodium falciparum* infections cause significant amounts of parasite-infected red blood cells, which in persons who have never experienced malaria, cause widespread inflammation and high temperature according to Surette et al. (2021). Paroxysmal fever from malaria infection is caused by potent pro-inflammatory reactions including pyrogenic cytokines like IL-1 β and TNF- α says Clark et al. (2006). Unexpectedly, only IL-6 showed an association with parasitemia load in the research conducted by Oyegue-Liabagui et al., (2023), whereas, IL-6 and IL-10 had only a weak relationship with temperature, a discovery comparable to the study of Hugosson et al., (2006) who noted that body temperature was linked to the levels of IL-10, IFN- β IL-6 and IFN- γ , and IL-6, and parasitemia with levels of IL-6 and IL-10 in children with acute, uncomplicated *P. falciparum* infection. In persons with malarial anemia, it was noted that IL-6 and IL-10 levels were significantly greater in severe malarial anemia than in simple malaria, which suggests that these

cytokines are produced during *P. falciparum* malarial anemia and are involved in the pathogenesis (Mandala et al., 2017; Oyegue-Liabagui et al., 2017).

Generally, malaria infection is accompanied by symptoms such as; convulsions, hemolytic anemia, hemoglobin in the urine, jaundice, headache, fever, shivering, joint pain, vomiting (Beare et al. 2006), and paroxysm.

Complications

The research conducted by Danny et al. (2015) have suggested that imbalanced inflammatory responses particularly during high parasitic burden can aggravate the malaria clinical manifestations and results in severe pathological complications such as severe anemia (SA), acute respiratory distress syndrome (ARDS), acute renal failure (ARF), and cerebral malaria (CM). The possibility of enlarged spleen, liver, or both, chronic headache, hypoglycemia, and the presence of haemoglobin in urine and renal failure have also been reported (Bartoloni and Zammarchi, 2012).

Diagnosis

A microscopic observation of blood films or antigen-based rapid diagnostic tests (RDT) are typically used to confirm malaria parasite infection. The gold standard for diagnosing malaria is microscopy, which involves investigating Giemsa-stained blood under a light microscope (Ashley et al., 2018). The laboratory scientists often check both a "thick film" of blood which enables them to quickly scan a large number of blood cells and a "thin film" of blood that allows them to visualize individual parasites clearly to determine the Plasmodium species that responsible for the infection. When there are at least 100 parasites per microliter of blood, which is approximately the lower range of symptomatic infection, the observer can detect parasites under standard field laboratory conditions.

According to the WHO report on Global Malaria Program 2021 (WHO, 2021), the detection of malaria infection on the basis of the parasitic infection allows medical professionals to quickly differentiate between malarial infection and non-malarial fevers, enabling for the most effective therapy, which lowers morbidity and death. It enhances the general care of patients with febrile infections and might also aid in halting the development and spread of drugs resistance.

Treatment

According to the study carried out by Hanboonkunupakarn and White (2022), antimalarial drugs are employed in the treatment of malaria, and the type and strength of the medication used will depend on the type and severity of the infection. Artemisinin-based medications are effective as well as safe for the treatment of uncomplicated malaria. When administered to treat uncomplicated malaria, artemisinin-combination therapy, also known as ACT, or artemisinin-combination therapy, is approximately 90% successful (Howitt et al. 2012). Pousibet-Puerto et al. (2016), and Kokwaro (2009) reported that, ACT is the most effective way to treat *P. falciparum* infections since it reduces resistance to any individual drug component.

Other recommended effective anti-malarial drugs for uncomplicated malaria include; Artemether-lumefantrine (six and four dose regimen) (Omari et al., 2006), combination of dihydroartemisinin and piperaquine (Keating, 2012), Artemisinin-naphthoquine combination therapy (Isba et al., 2015) and numerous others.

Sinclair et al. (2012) suggested the use of intravenous anti-malaria treatment for severe anti-malarial infection. Also, parenteral artesunate was found to outperform quinine in the treatment of severe malaria with respect to both children and adults.

Emerging Therapies

A clinical trial conducted in 2022 with monoclonal antibody mAb L9LS revealed they were able to offer protection against malaria, via binding with the *Plasmodium falciparum* circumsporozoite protein (CSP-1), which is necessary for the illness, rendering it inactive (Lab-made antibody stops malaria, 2022).

Medicinal Plants

A research carried out by Funmilayo et al. (2020) on cytokine modulation during malaria infection by some medicinal plants showed that extracts of medicinal plants such as *Morinda lucida*, and *Nauclea latifolia*, among several others, was effective against *Plasmodium parasite*. According to this study, *Morinda lucida* was found to notably stimulate pro-inflammatory and anti-inflammatory cytokines, which are crucial for malaria pathogenesis and prophylaxis. *Nauclea latifolia* on the other hand was found to considerably increase the pro-inflammatory (IL-6, IL-12, and TNF- α) and anti-inflammatory (IL-10) rate of cytokines also.

Table 1. Pre-treatment and post-treatment cytokine outcome of aqueous extracts
Percentage Immunomodulation of the different aqueous crude extracts after treatment.

Extracts	Percentage Immunomodulatory activity of cytokines (%)					
	IL-6	MCP-1	IFN- γ	IL-10	IL-12p70	TNF- α
Empty Cell						
<i>M. lucida</i> (l)	10.9	-15.5	3.41	-0.98	-14.6	-9.06
<i>M. lucida</i> (sb)	69.6*	87.2*	27.7*	38.3*	81.4*	45.0*
<i>N. latifolia</i> (l)	43.2*	-4.29	-5.74	1.50	9.24	-3.25
<i>N. latifolia</i> (sb)	16.9	-13.9	-14.3	0.41	8.31	-1.16
<i>T. diversifolia</i> (l)	12.9	-29.2	-16.4	-5.87	-22.1	-8.89
<i>L. inermis</i> (l)	35.3*	-0.94	-8.38	6.84	-18.7	3.46
<i>C. odorata</i> (l)	9.99	-2.73	0.67	0.41	5.84	9.35
Control	—	—	—	—	—	—

Legend: *Indicates significant difference from control, $p \leq 0.05$; l = leaves, sb = stem bark.

Pro-inflammatory cytokines (IL-6, IFN- γ , IL-12p70, and TNF- α) as well as anti-inflammatory cytokines (IL-10) and chemokines (MCP-1) were all considerably

elevated by *M. lucida* stem bark extract. The degree of the cytokines' immunomodulatory activity after therapy with it was between 27.8 and 81.4%. On the various cytokines, all other extracts either expressed stimulatory or down-regulatory properties (Funmilayo et al., 2020).

Another research conducted by Mohanty et al. (2021) on the efficacy of Ellagic acid (EA) on chronic malaria pathogenesis through cytokine storm and oxidative stress reduction revealed that, Ellagic acid was able to drastically lower parasitemia, while at the same time lowering the cytokine storm and oxidative stress in the vital organs of the test subjects.

Prevention

Malaria can be prevented through the use of treated mosquito nets, indoor residual spraying, living house modification (Fox et al., 2022), clearing of stagnant waters, drainages, and water supply and bushes around living areas.

3. Conclusion

In summary, cytokines are essential for controlling the disease's magnitude, parasite burden, and symptomatology in malaria. This research has also proven that malaria parasite infection is linked to the significant higher levels of IL-6 and IL-10 cytokines people with symptomatic malaria, whereas the levels of IL-12p70, IL-13, and IL-22 were elevated in those who were asymptomatic.

It was also discovered in this study that only IL-6 showed an association with respect to parasitemia load, and in persons with malarial anemia, it was noted that IL-6 and IL-10 levels were significantly greater in severe malarial anemia than in simple malaria.

This review also discovered that imbalanced inflammatory responses particularly during high parasitic burden can aggravate the malaria clinical manifestations and results in severe pathological complications such as severe anemia (SA), acute respiratory distress syndrome (ARDS), acute renal failure (ARF), and cerebral malaria (CM), and possibility of other chronic health conditions such as swollen spleen, renal failure, and chronic headache.

Finally, this study showed the efficacy of natural regimen on suppressing malaria infections, increasing cytokine levels, as well as, offering protection from cytokine storm where where necessary.

Recommendation

More research towards better comprehension of the cytokine's role in the pathogenesis of malaria should be conducted, with the intent to making new of new malaria vaccines especially with natural regimens in focus, diagnostic markers, and indications of the extent and development of the disease.

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