Chapter 5

Multiple Organ Dysfunction During Severe Malaria: The Role of the Inflammatory Response

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Abstract

Severe malaria is a systemic illness characterized by the dysfunction of one or more peripheral organs, such as the lungs [acute respiratory distress syndrome (ARDS)] and kidneys [acute kidney injury (AKI)]. Several clinical and experimental studies suggest that features of the inflammatory response are related to the multi-organ dysfunction observed in severe malaria. Our group has been dedicated to studying the roles of pro- and anti-inflammatory mediators in the multi-organ dysfunction observed in experimental severe malaria, especially in the lungs, kidneys, and brain. Herein, we explore severe malaria as a pathology derived from intense inflammatory responses in different organs and further distinguish and compare these organ-specific inflammatory responses. The pathophysiological mechanism of severe malaria is not fully elucidated; however, it is important to study it as a complex inflammatory response assembled by different actors, each one orchestrating a different mechanism.

Keywords: inflammation, cerebral malaria, acute respiratory distress syndrome, acute kidney injury, vascular permeability

1. Introduction

Severe malaria is a systemic illness characterized by one or more clinical manifestations, such as acute respiratory distress syndrome (ARDS), multiple convulsions, prostration, shock, abnormal bleeding, jaundice, and acute kidney injury (AKI) [1–3]. Severe malaria used to be exclusively attributed to *Plasmodium falciparum* infection. However, in the last 15–20 years,

several reports of severe malaria attributed to *Plasmodium vivax* [4–6] and *Plasmodium knowlesi* [7–9] have been described, which led the World Health Organization (WHO) to add these species as causes of severe malaria [10]. According to the WHO, severe malaria evolves from an uncomplicated illness due to several factors, such as the host response, parasite virulence, comorbidities, and deficient health services for malaria patients. Beyond the three species cited above, *Plasmodium malariae* and *Plasmodium ovale* also affect multiple organs in children and adults, however with different intensity (**Table 1**). The multi-organ dysfunction observed during severe malaria is associated with a systemic inflammatory response triggered by, among other factors, leukocyte adhesion to organ microvasculature, parasitized erythrocytes and production of inflammatory mediators [11, 12]. Despite the morphological and biochemical differences among *Plasmodium* species, the mechanisms by which severe malaria develops appear to be similar. Herein, we discuss the inflammatory response underlying the Physiopathology of severe malaria in human and experimental data. We further discuss triggers of the inflammatory response and how chemical and cellular mediators of inflammation cause severe malaria-induced multi-organ damage [6, 7, 9, 13–36].

	Clinical manifestation			
	ARDS	CM	Jaundice	AKI
Species				
P. falciparum	[13, 14]	[13, 15–22]	[13, 14, 16, 17, 23]	[13, 14, 16, 18, 24]
P. vivax	[6, 23, 25–27]	[27]	[6, 23]	[6, 18, 27]
P. knowlesi	[9, 28, 29]	–	[32, 36]	[31, 32, 36]
P. malariae	[31]	[6, 18, 27]	[7, 28–30]	[31, 32, 36]
P. ovale	[31, 33, 34]	–	[33, 35]	[31, 35]

ARDS, acute respiratory distress syndrome; CM, cerebral malaria; AKI, acute kidney injury.

Table 1. Studies describing severe malaria clinical manifestation according *Plasmodium* species.

2. Molecular and cellular features of the malaria-induced inflammatory response

During severe malaria, leukocytes and lymphocytes produce soluble inflammatory mediators, such as pro-inflammatory cytokines, which activate endothelial cells [37]. Furthermore, proteins anchored on membranes of infected red blood cell (RBC) such as *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), expressed by parasites, induce endothelium activation resulting in increased expression of adhesion molecules [38, 39] and the activation and adhesion of leukocytes to the microvasculature.

In both the pre-erythrocytic and erythrocytic phases, macrophages and monocytes are responsible for the cytokine storm during an acute malarial infection [40]. Activation of

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phagocytes is mediated by binding of the hemozoin/parasite DNA complex to TLR-9 and the consequent downstream activation of inflammasome signaling [41]. The hemozoin released into circulation during infected RBC lysis is taken up by circulating monocytes and tissue macrophages and activates inflammasome intracellular protein complexes, such as NOD-, LRR-, and pyrin domain-containing (NLRP)3 and NLRP12, resulting in caspase 1 activation and the subsequent release of interleukin (IL)-1β, which is involved in fever during malaria bursts [40, 42]. In addition to inducing pro-inflammatory cytokines, some studies demonstrate that hemozoin can also induce the expression of anti-inflammatory cytokines in monocytes, such as IL-10, which tightly regulates IL-12 and CCL5 production [43]. These cytokines and chemokines, respectively, are directly involved in the development of the immune response [44]. Mononuclear cell activation leads to the production of TNF-α and IL-12 by neutrophils. These cytokines stimulate innate immune cells, such as natural killer (NK) cells and γδ T cells (including γδ NKT cells), to rapidly produce IFN-γ. As a consequence, IL-12 and IFN-γ activate monocytes and macrophages to enhance the phagocytosis of infected RBCs (reviewed in [45, 46]) and produce reactive oxygen and nitrogen radicals, which kill parasites [47].

The activation of the cellular components of the innate immune system, such as dendritic cells (DCs), is important for the establishment of acquired immunity [40]. In the spleen, DCs present their processed antigens to naïve T cells (Th0) and induce a pro-inflammatory response (Th1) with mainly $CD4^+$ T cells that produce IFN-γ. This lymphocyte subtype is involved in the beginning of malarial infection by further stimulating Th1 differentiation and subsequently stimulating B cells to produce specific antibodies to eliminate malaria parasites [46]. In addition, $CD8^+$ T cells act in the effector phase, contributing to permeability changes in the blood-brain barrier (BBB) through perforin-dependent mechanisms [48].

Beyond leukocytes and lymphocytes, endothelial cells also play a crucial role in the inflammatory response during severe malaria. In the erythrocytic phase, endothelial activation accounts for many factors involved in the development of severe malaria [49], such as increased adhesion of infected RBCs [50], increased expression of chemokines [51], and increased adhesion of leukocytes to peripheral organ microvasculature [52]. Several soluble proteins have been described such as inflammatory markers of endothelial activation during severe malaria. The angiopoietin (Ang)-Tie2 axis is a critical regulator of endothelial quiescence, activation and dysfunction in infectious and oncologic diseases, atherosclerosis, and pulmonary hypertension [53, 54]. Ang-1 signals through its cognate receptor Tie-2 (a tyrosine kinase with immunoglobulin and endothelial growth factor homology domains), which is expressed on endothelial cells [53]. In addition, Ang-2 (partial/weak agonist of Tie-2) is released by endothelial cells and acts as an Ang-1 antagonist [55]. During cerebral malaria (CM), Ang-1 exerts anti-inflammatory effects by decreasing adhesion molecule expression and maintaining the integrity of the BBB by reinforcing VE-cadherin tight junctions [53, 54]. In contrast, Ang-2 is stored in Weibel-Palade bodies (WPB) within endothelial cells and is involved in the response to inflammatory stimuli. High levels of Ang-2 are observed in children with severe malaria [56]. In healthy subjects, the basal Ang-1 level is higher than that of Ang-2, while the opposite ratio is observed in fatal cases of severe malaria [57]. Another inflammatory marker of endothelial activation during sever malaria is the activation of endothelial cell protein C

receptor (EPCR). EPCR is widely expressed on endothelial cells and leukocytes, and its activation is associated with severe malaria [58, 59]. EPCR is referred to as the cell surface conductor of cytoprotective coagulation factor signaling because it enhances the conversion of protein C into its activated state, activated protein C (APC). The EPCR/APC complex has anti-inflammatory and endothelial cytoprotective activities that help maintain vascular integrity [60, 61]. The binding of infected RBCs to EPCR impairs the formation of the EPCR/APC complex, which may lead to sequestration, complement activation, and endothelial dysfunction, as reflected by Weibel-Palade (WP) body exocytosis, with the release of von Willebrand factor (vWF) and angiopoietin-2 and the increased expression of other endothelial receptors, such as ICAM-1 [60].

3. Organ-specific inflammatory responses

The inflammatory features described above occur in different organs and at different intensities. Although there are few examples of leukocyte adhesion in the brain vasculature in the development of human cerebral malaria [62], necropsy in fatal cases of severe malaria reveals marked inflammatory cell infiltration in lung tissue [11]. Endothelium/leukocyte interactions in the lung differ from their interactions in the brain, likely due to differences in the BBB and the blood-air barrier tight junction compositions of the brain and lung endothelium. However, the malaria-induced inflammatory response that is responsible for kidney dysfunction is not related to inflammatory cell accumulation in renal tissue but depends on immunocomplex deposition and infected RBC adhesion to the renal vasculature [63].

3.1. Inflammatory components in the development of cerebral malaria

Cerebral malaria is mainly attributed to *P. falciparum* infection, especially in children under five years [64]. Cerebral complications during malaria are triggered by the mechanisms described above; however, the inflammatory response observed in the brain is unique.

Taylor and coworkers have been studying the pathogenesis of cerebral malaria (CM) and have observed three different pathologies: (i) CM1—presence of sequestered parasitized erythrocytes in the cerebral microvasculature; (ii) CM2—presence of sequestered parasitized erythrocytes in the cerebral microvasculature and vascular pathology; and (iii) CM3—non-malarial components involved in cerebral damage. Inflammatory mediators are involved in CM1 and CM2. As described above, adhesion molecules and EPCR expressed in brain endothelial cells induce parasitized erythrocyte adhesion [58]. Likewise, during CM2, leukocytes are observed in the intravascular space, and plasmatic proteins are found in the brain tissue, suggesting edema formation [62]. The role of leukocytes in the pathogenesis of cerebral malaria is unclear. A main characteristic of brain anatomy is the presence of the BBB, which confers protection against circulating cell diapedesis into brain tissue. Nevertheless, the BBB composition of postcapillary venules allows leukocyte diapedesis during non-malarial brain injury [65, 66]. However, leukocytes are not observed within brain tissue during CM2 [62, 67], suggesting an indirect contribution of these cells to the development of cerebral malaria. Cytokine production

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by leukocytes during *P. falciparum* infection may contribute to brain endothelial cell activation, indicating that leukocyte involvement in cerebral malaria does not depend on cell-cell contact [68, 69]. Wassmer and colleagues hypothesized that higher endothelial responses to TNF-α increase the probability of a patient developing cerebral malaria. The authors suggest that endothelial activation by TNF-α increases the expression of adhesion molecules, which facilitates the binding of parasitized erythrocytes, leading to CM1/CM2. Thus, CM1/CM2 is a pathogenesis triggered by parasitized erythrocytes but sustained by a local inflammatory response (**Figure 1**).

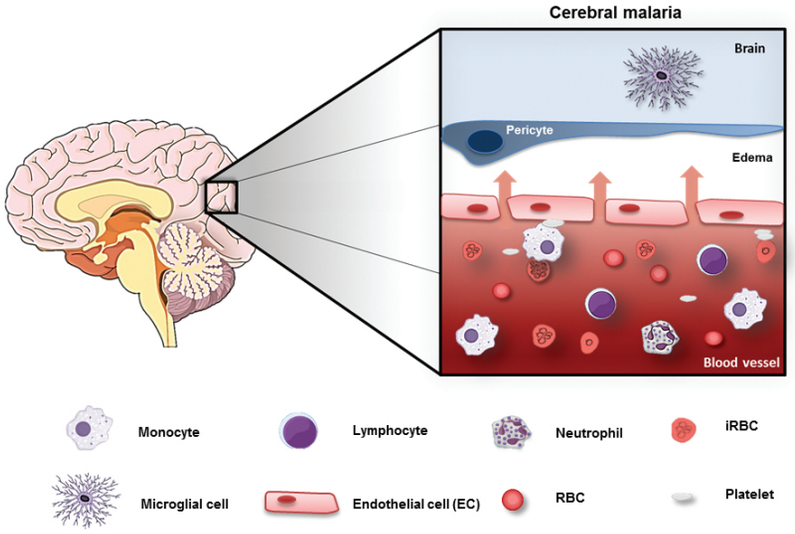

Figure 1. Inflammatory response during cerebral malaria—during cerebral malaria, it is possible to observe the presence of sequestered parasitized erythrocytes in the cerebral microvasculature, vascular pathology, leukocytes in the intravascular space and plasmatic proteins in brain tissue, suggesting edema formation. Figure created in the Mind the Graph platform (www.mindthegraph.com).

Although experimental models of severe malaria could not be used to predict human pathology, they have been extensively used to elucidate cellular and molecular pathophysiological processes. Several findings observed in human cerebral malaria are also observed in experimental models, including cytokine activity [70], endothelial activation [71], and edema formation [72]; however, the sequestration of parasitized erythrocytes during experimental cerebral malaria (ECM) is not well understood. Recent evidence showed that *Plasmodium berghei*-ANKA infected RBCs adhere to brain microvascular endothelial cells in a VCAM-1-dependent manner [73]. In addition, another study suggests transient contact between infected RBCs and the endothelium [74]. The expression of Pf-erythrocyte membrane protein (EMP)s and their ability to adhere to host adhesion molecules depends on the expression of structural proteins, such as knob-associated histidine-rich protein (KAHRP), that allow the formation of knobs on erythrocyte membranes [75]. *Plasmodium* species incapable of forming knobs in infected erythrocytes (knobless *Plasmodium*) show a passive adhesion of infected RBCs to activated endothelial cells [75]. Thus, knobless *Plasmodium* activates endothelial cells to the same extent as knob-forming *Plasmodium* [66, 73], which suggests that ECM may also be induced by parasitized erythrocytes.

The participation of leukocytes and lymphocytes in ECM has been extensively described [76]. Different from that observed in humans, during ECM, the adhesion of leukocytes and lymphocytes in the brain vasculature is well described [71, 74, 77]. In fact, monocytes, $CD4^+$ T cells, $CD8^+$ T cells and platelets adhere in brain post capillary venules but do not transmigrate to the brain tissue of *P. berghei* infected mice, supporting the idea that the brain disorder is due to leukocyte induced-endothelial dysfunction. Thus, strategies targeting endothelial stabilization revert ECM and prolong survival in mice [71, 78].

3.2. The inflammatory response in severe malaria-induced ARDS

Beyond the brain, the lungs are the most affected organ in severe malaria. Lung dysfunction occurs in 20% of all cases of adults with falciparum [3] or vivax [27] severe malaria. In knowlesi severe malaria, more than 50% of patients develop acute respiratory distress syndrome (ARDS) (reviewed in [3]). Recently, the methods for ARDS diagnosis are redefined, and ARDS is now classified as mild, moderate, or severe according to chest imaging, the origin of edema, oxygenation, and respiratory dysfunction timing [79], which supports the idea that the epidemiological data regarding malaria-induced ARDS may be underestimated. Nevertheless, ARDS can be caused by direct lung injury (pulmonary infection, aspiration, lung contusion, etc.) or by indirect lung injury (systemic inflammation, transfusion, burn injury, etc.) (reviewed in [80]). Thus, during severe malaria, lung dysfunction can be triggered directly by adhesion of infected RBCs to the lung vasculature or indirectly as a consequence of the activity of endothelial activators (**Figure 2**).

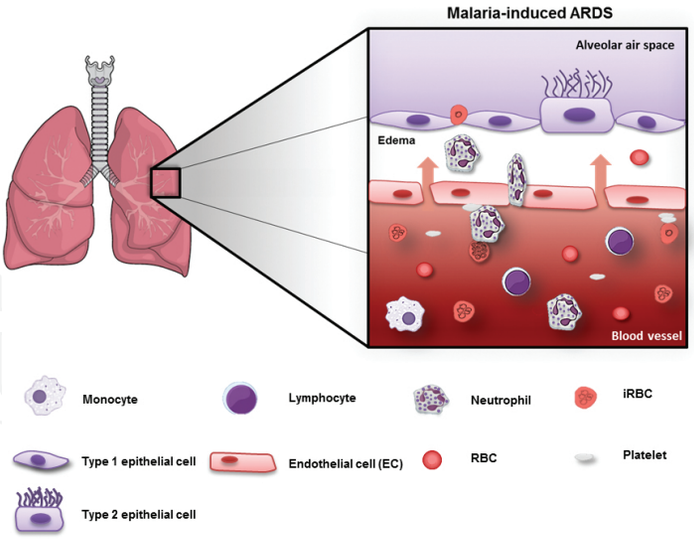

Figure 2. Inflammatory components observed in severe malaria-induced ARDS—in the lungs of patients with severe malaria who develop ARDS, increases in vascular permeability, infected erythrocytes, and intense neutrophil infiltration are often observed. Figure created in the Mind the Graph platform (www.mindthegraph.com).

Although CM is common in children, ARDS is often observed in adults [81]. In fact, the pathology observed in the lung tissue differs between adults and children. In children, few cases of pneumonia are observed [11], while an intense inflammatory cell infiltration is

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frequently noted [11, 82]. Milner and coworkers hypothesize that ARDS in children is an indirect effect of the inflammatory response induced by CM because non-specific lung dysfunction is observed. In fact, it has already been demonstrated that the inflammatory response triggered by brain injury directly affects the respiratory system by altering vascular permeability and allowing leukocyte influx into the lung parenchyma [83]. However, in adults, the presence of infected RBCs likely induces a local inflammatory response. Gillrie and coworkers proposed that merozoite-derived histones bind to pathogens-associated molecular patterns (PAMPs) expressed on endothelial cell membranes, leading to MAPK activation and the consequent production of pro-inflammatory mediators. In addition to the production of inflammatory mediators, *Plasmodium* also induces cell death and alterations in the expression of junctional proteins, which facilitates the influx of leukocytes to pulmonary tissue [84, 85].

Experimental models of severe malaria have revealed that ARDS begins when merosomes activate endothelial cells within pulmonary capillary beds [86, 87]. Thus, some authors suggest that the erythrocytic cycle starts in the lung capillaries [86]. In addition to merosomes, hemozoin and the close contact between infected erythrocytes and pulmonary endothelial cells trigger an inflammatory response 24 h after infection. This is characterized by intense leukocyte infiltration, as well as the production of proinflammatory mediators in the lung tissue, which persists for at least five days after infection [88–91]. Different from that observed in brain pathology, the inflammatory cellular infiltration in the lungs is mainly composed of neutrophils [90]. In fact, depletion of neutrophils impairs experimental severe malaria-induced ARDS and prolongs survival in mice [92, 93]. The participation of leukocytes in lung dysfunction during malaria may be explained, in part, by their interaction with the endothelium. In the brain, there is no leukocyte transmigration, while in the lung, tight junctional constitution and adhesion molecules expressed in the endothelium allow leukocyte transmigration and the consequent accumulation of these cells in the lung parenchyma. Thus, despite constitutional differences, the preservation of endothelial integrity in both the lungs and the brain may contribute to the attenuation of severe malaria symptoms.

3.3. The inflammatory response observed in severe malaria-induced acute kidney injury

Systemic disorders often result in secondary damage, such as functional and structural changes in the kidneys and consequent acute renal failure (ARF). The term ARF was replaced by the term acute kidney injury (AKI), which represents more than renal failure characteristics, according to the risk, injury, failure, loss, and end-stage renal failure (RIFLE) criteria [94, 95]. At present, the RIFLE criteria are widely used to diagnose AKI [96]. Severe malaria-derived AKI (smAKI) is more common in adults than in children [81]. Beyond the AKI reported in severe cases of *P. falciparum* and *P. vivax* malaria [97, 98], there have previously been reports of AKI in conjunction with the rare complications derived from infection with *P. ovale*, *P. malariae*, or *P. knowlesi* [35, 99, 100]. AKI is diagnosed in almost 50% of severe malaria cases. Currently, smAKI is diagnosed according to the WHO 2006 criteria; however, Thanachartwet and colleagues suggest that, according the RIFLE criteria, these numbers are underestimated. Instead, according the RIFLE criteria, almost 75% of severe malaria patients are developing AKI [96].

The pathophysiology of smAKI is still unclear. Because AKI can develop as a secondary effect of a systemic disease, some authors suggest that the systemic inflammatory response induced in peripheral organs during severe malaria contributes to smAKI development [101]. However, ultra-structural and histological studies of renal tissue in fatal cases of severe malaria reveal an intense inflammatory cell accumulation, indicating that smAKI can also be locally induced [18, 102].

In general, endothelial cell swelling, hypertrophy, and cytoplasmatic vacuolation suggest endothelial activation and are characteristic of smAKI [18, 102]. Such characteristics are similar between affected organs [3, 62]; however, unlike brain endothelial cells [103], kidney endothelial cells do not phagocytose infected RBCs. Regarding leukocytes, smAKI is characterized by the intense presence of mononuclear cells in peritubular capillaries, but not neutrophils, platelets, or eosinophils (**Figure 3**). Increased levels of plasmatic TNF-α [104], soluble urokinase-type plasminogen activator receptor (suPAR) expression [105], and mononuclear activation markers correlate with AKI in patients with severe malaria, suggesting that mononuclear activation induces tissue damage. Furthermore, mononuclear cells do not infiltrate the renal tissue interstitium as they do in the lungs [3], likely because, despite the activation of the renal endothelium, the tight junctions in renal tissue are not fully disrupted during severe malaria [106]. Another inflammatory characteristic that is mainly attributed to AKI is the deposition of immune complexes in the kidneys. The nephropathy associated with the deposition of immunoglobulin (Ig) isotypes G and M in the kidneys has previously been described in patients with severe malaria; however, the pathological events that result in immune complex deposition depend on the *Plasmodium* species and the time of patient death [107, 108].

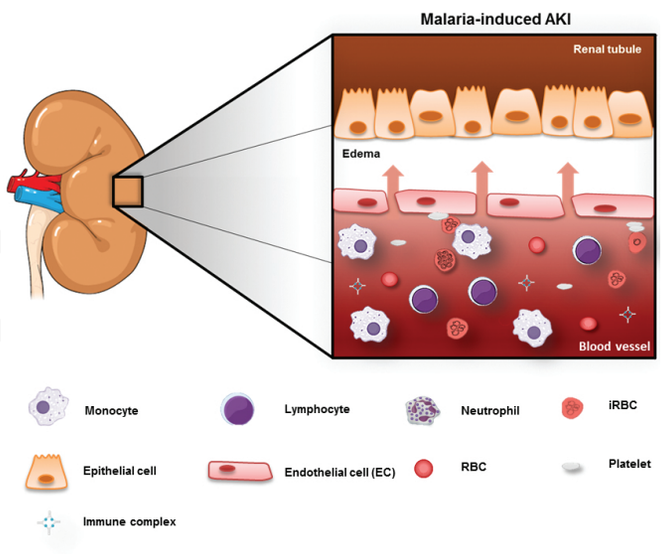

Figure 3. Severe malaria-induced AKI—during severe malaria-induced AKI, there is an intense mononuclear cell accumulation in renal tissue, endothelial cell swelling, hypertrophy, and cytoplasmatic vacuolation, suggesting endothelial activation. Different from that observed in the lungs and brain, this suggests that AKI results from deposition of immunoglobulins in the kidneys. Figure created in the Mind the Graph platform (www.mindthegraph.com).

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Inflammatory components of AKI are also observed in experimental models of severe malaria. Endothelial dysfunction assessed through the evaluation of increased vascular permeability [109] and the expression of adhesion molecules [110] is also observed in experimental models of severe malaria. The activation of the glomerular endothelium may be involved in the accumulation of inflammatory cells and infected erythrocytes in glomeruli [111]. Furthermore, inflammatory cells present in the kidneys produce pro-inflammatory cytokines that perpetuate renal damage [111]. In fact, studies in which mice were rescued from severe malaria, i.e., were cured of *P. berghei* infection, showed that renal dysfunction persists for at least 14 days after cure, suggesting that severe malaria-induced AKI is mainly sustained by inflammatory components [112].

Overall, further studies are required to unveil the pathophysiology of smAKI. To date, it is not clear how kidney tissue damage begins. SmAKI may be a secondary effect of the systemic inflammatory response, may begin locally, or may be the sum of both of these processes; however, once established, smAKI persists even after parasite clearance by antimalarial drugs [24], which raise the possibility for new therapeutic approaches that target the inflammatory response in the kidney.

4. Conclusions

The findings presented above show the influence of the inflammatory response in the development and perpetuation of severe malaria. It has been shown that *Plasmodium*-associated molecular patterns such as homozoin/parasite DNA and proteins expressed on membrane of infected red blood cells trigger inflammatory response including macrophage activation, T cell differentiation, endothelial cell activation, and the production of several pro-inflammatory mediators. *Plasmodium*-induced inflammatory response occurs systemically, however, due to different anatomical and physiological characteristics, each organ develops a particular

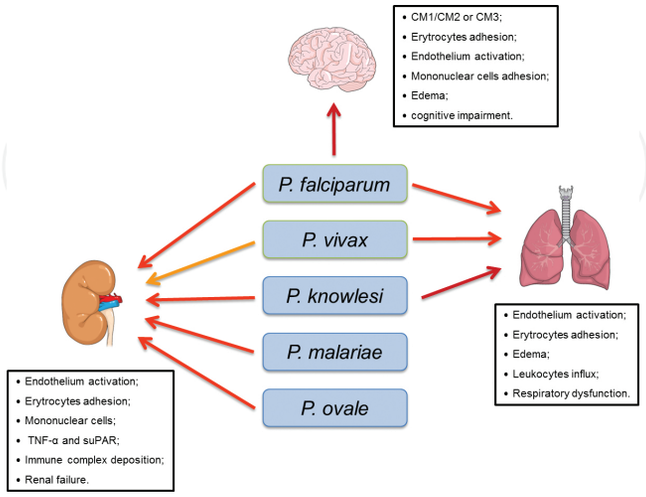

Figure 4. According to the WHO, severe malaria can be caused by *P. falciparum*, *P. vivax*, and *P. knowlesi*. However, the five *Plasmodium* species that infect humans are able to induce organ dysfunction due to a particular inflammatory response. Figure created in the Mind the Graph platform (www.mindthegraph.com).

inflammatory response that may lead to organ dysfunction (**Figure 4**). Although brain dysfunction is associated with activation of endothelial cells by the cytoadhesion of infected erythrocytes, severe malaria-induced ARDS is correlated with inflammatory cell accumulation in lung parenchyma.

Even though artemisinin derivatives are the treatment of choice for severe malaria, it accounts only for antimalarial purpose. In the last few years, host-directed therapies for malaria and other infectious diseases have been studied [113]. Several approaches aiming the inflammatory response have been studied in patients diagnosed with uncomplicated malaria [114, 115]; however, the treatment of severe malaria includes only supportive treatment. On the other hand, the use of experimental models of severe malaria suggested that the induction of cytoprotective pathways in brain as well the administration of anti-inflammatory drugs improve the survival of *P. berghei*-infected mice, especially when administrated as adjunctive treatment to antimalarial drugs [71, 76, 116, 117]. Indeed, a robust clinical evidence is yet necessary to provide the effectiveness of the treatment with inflammatory modulators as an adjunctive therapy to antimalarial drugs to improve patient outcomes.

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