

Malaria and COVID 19 Interactions: The Effects of the Collision of Two Giants

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Abstract

COVID-19 and malaria share similar pathogenic pathways with the angiotensin converting enzyme 2 as a central initiator of signals to stimulate host cellular responses which in some instances result in multi-organ affection. These signaling proteins are either upregulated or downregulated with the consequences of provoking immune responses with varying tissue damages. The similarities in clinical presentations, associated complications and therapeutic responses to the repurposed medications (anti-malarial drugs being used as anti-viral molecules) for the treatment of the novel disease COVID-19 have stimulated enormous interest in the recent past. The major objectives in this regard are to define the association between these two disease entities and possibly unveil options for interventions. This paper therefore aims at reviewing the molecular interactions which these diseases possibly share in their pathogenesis and phenotypic expressions and make projections for future interventions.

Key words: Malaria, COVID-19, Interactions, Effects, Collision, Giants.

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INTRODUCTION

Malaria Historical Antecedents

Malaria predates the prehistoric humans but it is thought to have originated in the tropics, precisely in Africa [1], and it was reported that the African region contributes 94% of the number of cases and deaths globally [2]. The Italians named the disease 'mal aria' which means foul air in the 18th century [1], while the early Asia-Hindu and Chinese writings made references to periodic fevers [1]. Hippocrates, the Greek Physician, described the clinical manifestations and some of the complications of malaria in the fifth century B.C [1]. Further work by South American researchers later revealed that the bark of the Peruvian Cinchona tree was successfully used for the treatment of intermittent fever in the early 17th century [1]. The active ingredient was subsequently found to be a quinine alkaloid which was isolated in France by 1820 [1].

Malaria parasite is transmitted through mosquito bites with different species of Plasmodium having been identified and these include; *P. falciparum* (responsible for >90% of infections and most dangerous), *P. malariae* (<10%), *P. ovale* (< 10%), *P. vivax*, and *P. knowlesi*. The Plasmodium parasites undergo asexual division in man and a sexual reproductive cycle in the anopheles mosquito [1].

The global malaria prevalence is about 300-500 million cases annually with 23 million of the patients living in Africa [2]. The African region carries a disproportionately high share of the global malaria burden, with 94% of malaria cases and deaths in 2019 [2]. On the other hand, Nigeria accounts for 25% of global malaria burden, with the under-5 children and pregnant women constituting the high-risk groups; in addition to accounting for almost 24% of global deaths from malaria [2].

Interaction of malaria parasite & host cells

Following mosquito bites, Plasmodium sporozoites are introduced into the peripheral blood and they invade erythrocytes and hepatocytes. Invasion of the erythrocytes is done through some receptors located on the surface of the erythrocytes cell membrane. The cascade of events that occur following the entrance of the Plasmodium into the cell is responsible for the clinical features of malaria. Red blood cells infected with *P. falciparum* occasionally sequester in the small capillaries and post-capillary venules of some tissues like the brain, lungs, spleen intestine, skin, fat tissue, bone marrow, and skeletal and cardiac muscles [3-10].

The role of Renin-Angiotensin system (RAS) in Plasmodium falciparum invasion of red cells

Plasmodium invades red blood cells through ACE2 receptors located on the red cell surface. Angiotensin II interacts with ACE2 receptor which converts it to Ang (1-7). Angiotensin-(1-7) binds to its specific receptor Mas which is expressed in the human erythrocyte membrane. A signalling pathway is triggered inhibiting PKA activity. Decreased PKA activity impairs merozoites invasion of the erythrocytes [11].

ACE polymorphisms are related to malaria severity by conferring protection from severe malaria in childhood [11]. Some studies have shown that the D

allele of ACE I/D polymorphism and ACE2 C→T substitution polymorphism which increase Ang II production are associated with mild malaria [11].

COVID -19

This is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in Wuhan city, China in December 2019. This disease has caused a pandemic resulting in over 123,902,242 confirmed cases of COVID-19 and 2,727,837 deaths across the globe [11]. Currently, healthcare delivery worldwide is enduring unprecedented strain. The diagnosis and management of SARS-CoV-2 has also faced some challenges in the malaria endemic zones because of the similarities in symptoms between SARS-CoV-2 and malaria [11].

Pathogenesis of COVID-19 infection

Severe acute respiratory syndrome Coronavirus-2 is transmitted through inhalation or contact with infected respiratory droplets [12]. The virus subsequently invades the host human cells by binding to angiotensin-converting enzyme 2 (ACE2) receptor especially on the type 2 alveolar cells in the lungs and other tissues which leads to affectation of the cardiovascular, neurological, haematopoietic, and the Immune system [13]. Coronavirus disease 2019 has impact on many laboratory parameters which have potential clinical and biological significance. (Table 1).

Table-1: Potential clinical and biological significance of abnormal laboratory values in patients with COVID-19 [19]

Laboratory parameter	Potential clinical and biological significance
Lymphopenia	Decreased immunological response to the virus
Leucocytosis	Bacterial (super)infection
Neutrophilia	Bacterial (super)infection
Increased value of monocyte distribution width	Severe viral infection/viremia/viral sepsis
Thrombocytopenia	Consumption (disseminated) coagulopathy
Increased value of CRP	Severe viral infection/viremia/viral sepsis
Increased value of procalcitonin	Bacterial (super)infection
Increased value of LDH	Pulmonary injury and/or widespread organ damage
Increased value of aminotransferases	Liver injury and/or widespread organ damage
Increased value of bilirubin	Liver injury
Increased value of creatinine	Kidney injury
Increased value of cardiac troponins	Cardiac injury
Decreased value of albumin	Impairment of liver function
Prolongation of prothrombin time	Activation of blood coagulation and/or disseminated coagulopathy
Increased value of D-dimer	Activation of blood coagulation and/or disseminated coagulopathy

CRP; C-Reactive protein, LDH; Lactate dehydrogenase

The role of ACE2 receptors in SARS-CoV-2 induced cytokine storm

SARS-CoV-2 spike proteins bind to ACE 2 receptors of numerous target cells like alveolar epithelial cells, macrophages, and blood circulating monocytes [17]. This induces exaggerated pro-inflammatory events through the activation of transcription nuclear factor kappa B (NFκ-B) intracellular signalling pathway leading to over

expression of pro-inflammatory cytokines and chemokines like IL-1B, IFN-γ, IL-6, IL-8, IL-12, IL-4, MCP1 and IL-10 in the serum [18]. Higher levels of other pro-inflammatory mediators including interleukin (IL)-2, IL-7, IL-10, tumour necrosis factor (TNF), granulocyte colony stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP1; also known as CCL2), macrophage inflammatory protein 1 alpha (MIP1α; also known as CCL3), CXC-chemokine

ligand 10 (CXCL10), C-reactive protein, ferritin, and D-dimers in serum have been in studies [19]. These findings suggest that severe COVID-19 can be identified by the presence of cytokine release syndrome, which is a disorder induced by cytokine

storms [20]. The excessive pro-inflammatory mediators cause vascular endothelial dysfunction which further leads to excessive thrombin generation and reduced fibrinolysis thereby creating a hypercoagulable state [21].

Table-2: Comparison of pathophysiology of malaria and COVID-19 [21]

COVID-19	Malaria
SARS-CoV 2 uses ACE2 receptor to achieve cell entry	Renin-Angiotensin System (RAS) derived peptides including ANG I, ANG II, MAS, ACE and ACE 2 may play a role in parasite development and in the regulation of the host immune response.
SARS-CoV 2 spike proteins bind to ACE 2 receptors, particularly the type 2 alveolar cells.	Malaria Associated symptoms may be controlled by host specific signalling pathways (e.g. PKA) that influence parasite invasion and development
Polymorphism or deletion of ACE2 gene plays an important role in geographical variations with respect to the prevalence of COVID-19.	ACE polymorphisms are associated with malaria severity i.e. they confer protection from severe malaria in childhood-higher levels of Ang II protect against cerebral malaria
They induce pro-inflammatory events through the activation of transcription nuclear factor kappa B intracellular signaling pathway leading to over expression of cytokines and chemokines (Cytokine storm).	Cytokine storm involving the ACE2 receptors in the bone Marrow and peripheral blood ultimately lead to depressed marrow function especially Lymphopenia and thrombocytopenia.

Table-3: Peculiarities between COVID-19 and Malaria [21]

	COVID-19	Malaria
Possible presentations	Asymptomatic, Presymptomatic, mild to critical, rapid progression to severe disease	Asymptomatic, mild to critical, rapid progression to severe disease
Common symptoms	Flu-like symptoms fever, headache, chills, myalgia, vomiting; diarrhoea and cough (commoner in children for malaria)	Flu-like symptoms fever, headache, chills, myalgia, vomiting; diarrhoea and cough (commoner in children for malaria)
Severe/Critical symptoms	Persistent pain or pressure in the chest ARDS Hypoxia Cyanosis Disseminated intravascular coagulation Death	Pulmonary complications ARDS Hypoxia, Cyanosis Multiorgan dysfunction and disseminated intravascular coagulation death Dehydration from excessive Vomiting Severe anaemia Prostration Convulsion(unconsciousness) Hyperbilirubinemia
Other symptoms	Loss of taste and smell	Taste impairment - Bitter or metallic taste
Outcome	Fatal in elderly, medical co-morbidities, mild in children More in densely populated / urban slums and in racial minorities (blacks, Hispanics)	Fatal in children, pregnant women, immune-compromised More in rural and densely populated / urban slums
Treatment	Empirical treatment with Hydroxychloroquine/chloroquine, Azithromycin, Ivermectin and other adjuvants	Chloroquine in countries where Plasmodium is still sensitive and artemisinin combination therapy in countries where there is chloroquine resistance

*ARDS (Acute respiratory distress syndrome)

Hypotheses on the relationship between malaria endemicity and coronavirus severity

Evolutionary adaptive changes such as variants of the ACE2 receptor, which is used by the coronavirus and malaria to infect cells, may protect populations from SARS-CoV-2 in malaria endemic regions [23]. Wide use of chloroquine and its derivative (hydroxychloroquine) in the prevention and treatment of malaria in sub-Saharan Africa may have also contributed to the protection against SARS-CoV-2 infection [24]. The mechanisms of action of these drugs include interfering in the glycosylation process of cellular receptors of coronavirus and increasing the endosomal pH thus inhibiting the fusion of the virus on the cells [25].

Use of Artemisinin in COVID-19

The COVID-19 pandemic has brought to light the need for continual search for medicines that have multiple pharmacological activities. One of such medicines or agents is artemisinin. Artemisinin and its derivatives is currently the mainstay for treatment of malaria albeit in combination with partner drug. The similarity of symptomatic presentation of malaria and COVID-19 early stages triggered a lot of trial use of known antimalarial drugs for the treatment of COVID-19.

In a non-randomized and controlled trial, patients with established diagnosis of Covid -19 were treated with Artemisinin-piperaquine against a controlled group treated with hydroxychloroquine. Participants were adult patients between ages 18 and above with confirmed SARS-CoV-2 infection in upper respiratory tract specimens by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR). The primary outcome were the time taken to reach undetectable levels of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the percentage of participants with undetectable SARS-CoV-2 on days 7, 10, 14, and 28. Outcome of study established a significantly shorter time to reach undetectable SARS-CoV-2 in patients with mild to moderate COVID-19 treated with Artemisinin-piperaquine compared to the control group treated with Hydroxychloroquine [26].

Impact of COVID-19 pandemic on malaria intervention programmes in Africa

The global malaria burden has been reduced in recent times following successful malaria control and intervention programmes. However, withdrawal of these interventions is likely to cause rapid resurgence of malaria and this threatens vulnerable population of pregnant women and children [27]. The COVID-19 pandemic brought about to a great extent a distraction from malaria management resulting in reduced availability of or distribution of malaria test kits. This was mainly due to lockdown-related disruptions to the

global supply chain [28]. Services such as seasonal malaria chemoprevention (SMC), distribution of insecticide treated nets (ITNs), malaria treatment and testing are disturbed due to risks of the COVID-19 infection to health workers who provide services during the pandemic [29]. Additionally, there were increased barriers to accessing healthcare during outbreaks following reduced transportation during lockdown. Some persons, especially daily wages earners had limited resources to pay to access the health facilities. Other negative impacts of COVID-19 on malaria intervention efforts include:

- Impairment of the malaria prevention campaign programs.
- Patients may stop visiting health facilities for malaria treatment as a result of fear of exposure to COVID-19 infection.
- Reduced accessibility of hospital facilities by patients due to lockdown of the regions.
- Diversion of government's attention from other pressing health challenges to COVID-19.
- Decreased availability of hospital infrastructure and consumables for management of severe malaria.
- Diversion of the inadequate health workforce towards COVID-19 care causing reduced manpower and attention to other illnesses like malaria.
- Widespread absenteeism due to illness of health workers.
- Absenteeism following restriction of human and vehicular movement by government.
- Misdiagnosis of malaria as COVID-19 by health workers.
- Missed diagnosis of malaria in COVID-19 patients.
- Inadequate personal protective equipment available for healthcare workers to manage other diseases.
- Impairment of medical supply chain due to deficiencies in logistics.

Studies had predicted that if concerted efforts are not made to strength the malaria control programmes, COVID-19-related disruption to malaria control in Africa could almost double malaria mortality in 2020, and potentially lead to even greater increases in subsequent years [30].

The role of Chloroquine (CQ) and Hydroxychloroquine (HCQ) in Malaria and COVID-19 comorbidities

The current knowledge of the role of both CQ and HCQ may be attributable to its wide use in malaria endemic countries. The somewhat chimeric or diverse inverse relation between COVID-19 and malaria prevalence may be referable to reports that these medications may have both preventive and curative effects against SARS-CoV-2 virus through several mechanisms:

- i. Immune modulation mechanisms that halt the disease progression and inhibiting cytokines storm by reducing T cell activation;
- ii. Changing cellular pH and preventing viral replication;
- iii. CQ has demonstrated antiviral activity in both infected and healthy cells which may apply also to HCQ.
- iv. (iv)They also inhibit the virus binding to its target host receptors (ACE2) as well as the membrane fusion [31]
- v. (v)The drugs can also alter glycosylation of ACE2 receptors by preventing receptor virus interaction, thereby reducing the binding affinity the virus spike proteins and cell receptors [31].

Through these processes, the drugs prevent viral entry into the cells. SARS-CoV-2 virus gains entry to the host cells through cellular structures known as endosomes. HCQ and CQ also achieve high concentrations within these lysosomes which cause an increase of pH from the low value obtained in the cell structures. The resultant effect is that the fusion of the virus with the endosomes becomes terminated [32]. The high pH creates an unfriendly environment for viral replication [33].

CONCLUSION

The significance of the shared peculiarities of the pathogenesis, immunomodulation and presentations and co-morbidities and mortalities of both SARS-CoV-2 and malaria infections, with the attendant impact on the logistics framework and architecture underline the need for urgent measures to mitigate its impact on critical global public health indices. In this regard, this ongoing pandemic may be beneficial in throwing up the opportunity to explore the possible role of previously well-documented anti-malarial drugs and molecules such as Artemisinins with reported anti-viral properties in the future treatment of SARS CoV-2 infections.

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