How COVID-19 and malaria are strikingly alike: A short review

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Abstract

COVID-19 is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that began in Wuhan, China, in late 2019 and has since spread globally, disrupting efforts to contain it. In Africa, the COVID-19 infection may be influenced by malaria coinfection. Global health is severely hampered by the co-infection of COVID-19 and malaria, especially in areas where both illnesses are endemic. Studies that have already been conducted indicate that those who have co-infection may have more severe symptoms and a higher risk of dying, even though there is little information on the prevalence and consequences of co-infection. More studies and focused initiatives are required to address this issue because of the difficulties in diagnosing the two diseases and the possibility that co-infection would worsen already existing health inequities. Methodology: This review follows the guidelines of PRISMA. In this article, we reviewed published articles from 2019 to May 2023 on COVID-19 and malaria co-infection that might influence the ontology of COVID-19. Results: Sub-Saharan African countries have fewer COVID-19 cases due to factors like young populations, warm weather, lack of proper diagnosis, malaria history, and antimalarial drug use. Population genetics also influence COVID-19 dynamics. Clinical and pathological similarities between malaria and COVID-19 have confused diagnosis and treatment in Africa. Conclusion: Understanding the dynamics of COVID-19 infection in Sub-Saharan Africa and how another endemic disease like malaria shapes it can provide insights into how to tailor successful diagnostic, intervention, and control plans that lower disease morbidity and mortality. Coinfection with COVID-19 and malaria is related to expanded all-cause in-hospital mortality compared to mono-infection with serious acute respiratory disorder coronavirus 2 (SARS-CoV-2).

Keywords: COVID-19; Malaria; Clinical Outcomes; Coinfection; Sub-Saharan Africa.

1. Introduction

Around 4 million people died and over 170 million became infected during the severe acute respiratory syndrome associated with the coronavirus (SARS-CoV-2) pandemic that started in Wuhan City, China, at the end of 2019 and spread to every part of the world. [1]. The Sub-Saharan region of central Africa, which has experienced decades of malaria endemicity, has a brittle and fragile health system [2]. The primary cause of deaths and cases in this region is a disease brought on by the protozoa Plasmodium falciparum, which is spread by female Anopheles mosquitoes [3]. The African region reported the fewest COVID-19 confirmed cases as of July 25, 2022 (9,187,634), followed by the Eastern Mediterranean region (22,490,905), and the European region (238,567,709) reported the highest number [4]. Malaria and COVID-19 can present with similar clinical symptoms, including but not limited to fever, backache, fatigue, shortness of breath, diarrhea, headache, stomach cramps, and muscle pain. [5]. There have also been illustrations of several other typical clinical, pathological, and immune determinant presentations. Due to these prevalent symptoms, diagnosis is difficult in areas with limited access to healthcare and facilities, and high throughput PCR testing, which is the method used worldwide, is not required for diagnosis. Once more, empirical treatments are frequently administered without laboratory testing (diagnosis) in most hospitals in Sub-Saharan Africa due to a lack of facilities and a high caseload. In both malaria-endemic and malaria-free zones, cases of malaria may therefore be misdiagnosed as COVID-
or vice versa, though concurrent infections have also been reported [6]. Many theories and postulations have been proposed to explain the low incidence of COVID-19 in African countries with high malaria burden and high incidence, as well as the delay in COVID-19 manifestation. These include low testing numbers, demographic factors, the role of climate, and travel patterns between Africa and the rest of the world (Figure 1).

Figure 1 Photomicrograph showing trophozoite of P. falciparum malaria. (A) thick blood smear. (B) thin blood smear. A specific quantity of Plasmodium parasites is visible on the viscous blood smear. The traditional, ring-shaped P. trophozoites. A thin blood smear revealed the falciparum parasite. (www.frontiersin.org)

1.1. Methods
This review follows the guidelines of PRISMA, PRISMA guidelines for review were employed in this study. Published articles from December 2019 to May 203 on COVID-19 and malaria co-infection and outcomes were searched in relevant and accessible databases.

1.2. Study inclusion and exclusion criteria
All accessible and available data published from 2019 to 2023 on COVID-19 and malaria was considered. Reports from post-mortem findings on COVID-19 and malaria co-infection were also included. studies on drug treatment for COVID-19 and malaria co-morbidity were included. In vitro, in vivo animals, and human studies on COVID-19 and malaria co-infection were excluded.

1.3. Search strategy and selection criteria
The search was performed in recognized electronic databases for peer-reviewed papers on the subject. Databases including Google Scholar, ResearchGate, PubMed, CINAHL, and Medline Plus were searched for studies published in any language. The search was performed by entering the following keywords (“Malaria and COVID-19, and Malaria and COVID-19 coinfection”) and included a broad derivative for wide search. We also retrieved articles with relevant and accessible abstracts with an unclear title. Other articles were manually searched, and references identified, and when appropriate, included in the review.

1.4. Genetic factors of Malaria and Covid-19
Among the most important variables influencing a disease’s susceptibility/resistance, course, and outcome are genetic factors. It can be stated that an individual's genetic protection against an infectious disease reflects their innate susceptibility to a potentially fatal illness [7]. Humans may naturally be resistant to SARS-CoV-2 infection to varying degrees; however, a sizable fraction of candidate genes that may be involved in this resistance have surfaced. In endemic areas, Plasmodium has exerted direct genetic pressure on numerous polymorphisms, leading to their selection. Angiotensin-converting enzyme 2 (ACE2) and viral spike proteins may interact similarly to cause COVID-19, according to recent research by Shang and colleagues [8]. This suggests that spike proteins play a crucial role in the attachment and entry of the virus. It has been shown that compared to Caucasians and different Asian populations, Sub-Saharan Africans exhibit higher levels of ANG II due to ACE1/D polymorphism. Furthermore, ACE2 expression is decreased due to a substitution polymorphism (C→T) in intron-1 of the ACE2 gene, which raises the level of AngII. Individuals with hypertension who have ACE2 (C→T) and ACE D/I polymorphisms may be protected against COVID-19 and malaria as a result of their lower ACE2 expression levels [9]. [Fig. 2].
Additional mutations or polymorphisms linked to malaria protection are probably going to make SARS-CoV-2 infection more susceptible and/or severe. A natural selection-driven mutation in glucose-6-phosphate dehydrogenase (G6PD) that protects against malaria in Africa and Asia may offer protection against parasite growth inside red blood cells (RBCs) or by triggering phagocytosis of infected cells early in the blood infection cycle. In response to microbial infection, G6PD indirectly regulates the innate proinflammatory-prooxidant and adaptive anti-inflammatory-antioxidant responses. This occurs as a result of glucose metabolism producing NADH, a cofactor needed to maintain equilibrium between the two reactions. As a result of the imbalance of both immune mechanisms caused by the deficiency in G6PD expression in SARS-CoV-2 infected individuals, the disease's severe outcomes are now affected [10].

1.5. Cellular invasion routes similarities between malaria and Covid-19

The universal consensus is that SARS-CoV-2 enters human cells through ACE-2. The virus's infection of erythroid progenitors (EPs) is amplified during the erythropoiesis stages using the highly expressed surface receptor ACE-2. Furthermore, the expression of certain receptors, such as CD27 and CD147, was observed early in the proliferation of EPs. It has been suggested by some researchers [11] that SARS-CoV-2 infection occurs via the erythrocyte surface receptor CD147, which targets nucleated bone marrow and young RBCs through endocytosis. Zhou et al. published a recent article. had demonstrated that a SARS-CoV-2 pseudovirus could infect the Vero E6 cells; however, this invasion was prevented when a CD147 knockdown cell was utilized in its place [12]. Notably, CD147 (also called Basigin or EMMPRIN) gives plasmodium a path to infiltrate red blood cells (RBCs); this process is facilitated by the blood-stage merozoite surface antigen PRH5[13]. A study that combines proteomics, metabolomics, and lipidomics was conducted on 29 COVID-19 patients in the United States as a complement to this. This study demonstrated that RBCs had a deformed cellular membrane, a disrupted glycolytic pathway within the erythrocyte, and a degraded N-terminal band 3 cytosolic domain. The possible invasion of erythrocytes by SARS-CoV-2 was the interpretation made for all these findings [14]. Remarkably, band-3 functions as a receptor for P's sialic acid-independent binding in human erythrocytes.

1.6. The roles of interferons and the neutralizing antibodies in malaria and COVID-19

Multivariate analyses have demonstrated that lymphocytes produced interferons in response to infection by multiple malaria strains; these interferons are effective against the coronaviruses that cause SARS, MERS, and COVID-19 both in vitro and in vivo [16]. Antibodies specific to Plasmodium antigens are developed by malaria patients. Some of these IgG antibodies target GPI molecules, which anchor certain Plasmodium species membrane proteins. Such "semi-immune" subjects have less severe clinical presentation than non-immune [17], even though prior malaria infection is not entirely
protective, as demonstrated by recurrent infections experienced by people in malaria-endemic areas. GPI mostly works by inducing leukocytes, which in turn causes the release of pro-inflammatory cytokines and increases adhesion molecule expression through Toll-like receptors 2 with 4. The harmful effects of Plasmodium GPI may be countered by anti-GPI antibodies. Furthermore, the glycoproteins (GPs) of SARS-CoV-2 are diverse, including membrane GPs, spike GPs, and GPs with acetyl esterase and haemagglutination characteristics. Anti-GPI antibodies can recognize these GPs, which can either create a milder disease pattern or provide protection against viral infection [18].

1.7. The use of hydroxychloroquine and chloroquine in COVID-19

The widespread use of hydroxychloroquine (HCQ), chloroquine (CQ), and other anti-malarial medications in nations where malaria is endemic is attributed by some scientists to the inverse relationship between COVID-19 and malaria [19]. The fact that research has been done on the effectiveness of HCQ and CQ in treating coronavirus diseases since the initial SARS outbreak should not be overlooked [20]. An ideal regimen for treating SARS-COV2 could involve 400 mg of HCQ per day for ten days, according to certain previous research that emphasized the significance of HCQ in this regard [21]. However, according to recent clinical studies, HCQ for SARS-Cov-2 should be used at a loading dose of 400 mg PO twice on the first day and then 200 mg every 12 hours for the next four days [22]. According to a reported clinical trial, using CQ or HCQ in COVID-19 carries more risks than benefits, as of May 22, 2020. However, the editor of The Lancet Journal has stated that data concerns will cause the article to be withdrawn [23]. The use of CQ and its derivatives is still widespread in malaria-endemic countries, despite WHO recommendations and drug resistance. For these reasons, some scientists view the use of anti-malarial medication as inadvertent chemoprophylaxis against SARS-CoV-2 [24]. According to some scientists, administering CQ and its derivatives as a preventative drug could lessen the spread of the coronavirus among healthcare personnel. They took into account how widely accessible the medication was.

1.8. How Covid-19 can affect the implementation of the malaria programs

In sub-Saharan Africa, malaria is a widely endemic disease. Approximately 600,000 lives are saved and nearly 100 million new cases of malaria are prevented annually by malaria control measures that are provided through public health facilities. The COVID-19 pandemic may cause disruptions in the healthcare delivery system, ineffective treatment, and untreated malaria cases, which could raise mortality and morbidity rates. The number of deaths from malaria outnumbered those from the Ebola virus because of the disruption to the health delivery system during the outbreak [31]. Ensuring that pregnant women and young children have access to core malaria prevention measures is crucial to easing the burden on health systems. These measures include chemoprevention for malaria in pregnancy and early childhood (seasonal malaria chemoprevention; SMC), as well as vector control strategies like indoor residual spraying and insecticide-treated nets (ITNs). Presumptive treatment for malaria and mass drug administration are additional steps that could lessen the strain on health systems in the context of COVID-19.

2. Discussion

Health systems around the world are under additional strain due to the ongoing COVID-19 pandemic, particularly in nations with weaker health infrastructure. Preserving their citizens’ health against both established threats like malaria and newly emerging ones like COVID-19 is a double-edged sword for many nations, especially those in sub-Saharan Africa, which is home to over 90% of the world’s malaria cases and fatalities. Despite its Chinese origins, COVID-19 has spread throughout the world and is currently a global pandemic. Although extra-pulmonary symptoms are possible, patients infected with SARS-CoV-2 can present in a variety of ways, from asymptomatic to rapidly failing respiratory. Nonetheless, the most typical symptoms are still fever, dyspnea, sore throat, and coughing [32]. Though its ability to spread airborne is still debatable, the disease primarily spreads through respiratory droplets during close contact [6]. Other modes of transmission, primarily extra-pulmonary ones like fecal-oral, have also been reported in certain research [33]. Treatment recommendations for COVID-19 disease have not yet been established by consensus. Several treatment protocols have been implemented. Among these, the antimalarial medication hydroxychloroquine has demonstrated antiviral activity in vitro [34]. Hydroxychloroquine 400 mg BID on day 1, followed by 200 mg BID for 4 days, is the regimen that my hospital uses. In severe cases, or if there are changes to the chest CT scan, an antiviral medication is added.

**Highlights**

- The reported low incidence of COVID-19 in Africa may be related to malaria.
- The reported low COVID-19 fatality and incidence rate in malaria-endemic locations may be explained by cross-immunity, common immunodominant epitopes between malaria and COVID-19, and antimalarial medications.
Due to halted malaria control efforts, the number of malaria cases and fatalities during the COVID-19 pandemic may rise. There have been reports of co-infection between COVID-19 and malaria.

**Abbreviations**
- RT-PCR: Reverse transcription polymerase chain reaction
- COVID-19: Coronavirus disease 2019
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
- SMC: seasonal malaria chemoprevention
- IPTi: intermittent preventive treatment in infants
- IPTP: intermittent preventive treatment in pregnancy
- ITNs: insecticide-treated nets
- HCQ: hydroxychloroquine
- CQ: Chloroquine

### 3. Conclusion
Malaria is a potentially fatal disease caused by the Plasmodium parasite. This protozoan can genetically influence the host and define the genetic structure of the population. It may also influence the host's immune response to co-infection with other pathogens. The seemingly striking similarities between Covid-19 and malaria encourage further research into the immunology and genetics of these two microbes. Due to varying exposure to Plasmodium in endemic areas, some people may not develop such immunity. In addition, such studies will not only pave the way to understanding COVID-19 infection and its mechanism of action in malaria-endemic areas but also help develop and produce an effective vaccine for the long-term control of malaria. In addition, such studies will not only pave the way to understanding COVID-19 infection and its mechanism of action in malaria-endemic areas but also help develop and produce an effective vaccine for the long-term control of malaria.

**Compliance with ethical standards**

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**Disclosure of Conflict of Interest**
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Authors Contribution**
Dr. Sakarie Mustafe Hidig Coined the idea and wrote the manuscript. All authors approved the submitted version.

**References**


