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IMPACT OF COVID-19 AND MALARIA COINFECTION ON CLINICAL OUTCOMES

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Thesis presented as requirement for the PhD Degree by the Graduate Program in Health Sciences, School of Medicine, Pontificia Universidade Católica Do Paraná

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"Wherever the art of medicine is loved, there is also a love for humanity."

Hippocrates

Abbreviations list:

AKI: Acute Kidney Injury

bn: billion in numbers

CCDC: Chinese Centre for Disease Control and Prevention

CQ: Chloroquine

FMOH: Federal Ministry of Health

HCQ: Hydroxychloroquine

IDPs: Internally Displaced People

IPC: Integrated Food Security Phase Classification

IPT: Intermittent Preventive Treatment

IRS: Indoor Residual Spraying

IRC's: International Rescue Committee's

ISN: International Society of Nephrology

ITNs: Insecticide-Treated Nets

IQR: Inter-Quartile Range

IUGR: Intrauterine Growth Retardation

KDIGO: Kidney Disease Improving Global Outcomes

LBW: Low Birth Weight

LMICs: Low-And-Middle-Income Countries

MIP: Malaria In Pregnancy

MOH: Ministry Of Health

MVIP: Malaria Vaccine Implementation Program

PF: Plasmodium Falciparum

PUPCR: Pontifícia Universidade Catolica do Parana

PHEIC: Public Health Emergency of International Concern

PV: Plasmodium Vivax

R21: R21/Matrix-M

RDT: Rapid Diagnostic Test

RTS,S: RTS,S/AS01

RRI: Renal Research Institute

RT-PCR: Real-Time Polymerase Chain Reaction

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

SD: Standard Deviation

SSACs: Sub-Saharan African Countries

UCTC: Universal COVID-19 Treatment Center

WHO: World Health Organization

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Abstract:

Objectives: Despite the possibility of concurrent infection with COVID-19 and malaria, little is known about the clinical course of coinfected patients. We analyzed the clinical outcomes of patients with concurrent COVID-19 and malaria infection.

Methods: We conducted a retrospective cohort study that assessed prospectively collected data of all patients who were admitted between May and December 2020 to the Universal COVID-19 treatment center (UCTC), Khartoum, Sudan. UCTC compiled demographic, clinical, laboratory (including testing for malaria), and outcome data in all patients with confirmed COVID-19 hospitalized at that clinic. The primary outcome was all-cause mortality during the hospital stay. We built proportional hazard Cox models with malaria status as the main exposure and stepwise adjustment for age, sex, cardiovascular comorbidities, diabetes, and hypertension.

Results: We included 591 patients with confirmed COVID-19 diagnosis who were also tested for malaria. Mean (SD) age was 58 (16.2) years, 446/591 (75.5%) were males. Malaria was diagnosed in 270/591 (45.7%) patients. Most malaria patients were infected by Plasmodium falciparum (140/270; 51.9%), while 121/270 (44.8%) were coinfected with Plasmodium falciparum and Plasmodium vivax. The median follow-up was 29 days. Crude mortality rates were 10.71 and 5.87 per 1000 person-days for patients with and without concurrent malaria, respectively. In the fully adjusted Cox model, patients with concurrent malaria and COVID-19 had a greater mortality risk (hazard ratio 1.43, 95% confidence interval 1.21-1.69).

Discussion: Coinfection with COVID-19 and malaria is associated with increased all-cause in-hospital mortality compared to mono-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Keywords:

Clinical outcomes; Coinfection; COVID-19; Malaria; Mortality; Sub-Saharan Africa.

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1- Introduction:

On 31 December 2019, a cluster of pneumonia cases of unknown etiology was confirmed in Wuhan City, Hubei Province, China. On 9 January 2020, the Chinese Center for Disease Control and Prevention (CCDC) reported that a novel coronavirus (2019-nCoV) was detected as the causative agent, and by 17 January 2020, a total of 44 laboratory-confirmed cases infected with 2019-nCoV have been reported, 41 from Wuhan, China and three travel-associated to (two patients in Thailand and one in Japan). Most of the patients visited a local fish and wild animal market in Wuhan. Furthermore, the local food market was cleaned and closed to the public on 1 January 2020.[1-3] On 7th January 2020, the CCDC identified the causative virus from throat swab samples and was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), tentatively named by World Health Organization (WHO) as the 2019-new coronavirus (2019-nCoV).[4] Additionally, by the end of January 2020, the WHO declared that the SARS-CoV-2 outbreak constituted a Public Health Emergency of International Concern (PHEIC). On March 11, 2020, the WHO declared the novel coronavirus (COVID-19) outbreak a global pandemic.[5,6] On 5th May 2023, the WHO announced that the COVID-19 epidemic would no longer be listed as a public health emergency of international concern, more than three years after the first PHEIC alert in January 2020.[7,8] The first African case of SARS-CoV-2 was notified by Egypt on 14 February 2020, while the first case in Sudan was reported on 13 March.[9,10] Globally, as of September 2024, the WHO has reported over 776 million confirmed cases and 7,061,330 confirmed deaths from or with COVID-19. These numbers include 63,993 confirmed cases and 5,046 deaths from Sudan[8].

The spread of COVID-19 has been devastating for some low-and-middle-income countries (LMICs) around the world, including Sudan, where presumably much more than the reported

patients have succumbed to COVID-19. The challenges for public health were enormous, and COVID-19 has been a major obstacle to human development in Sudan. The health systems were overwhelmed by the effect of the COVID-19 pandemic which led to disruptions in access to essential health services. Poor healthcare literacy and false information spread through social media further compound the impact of COVID-19. For example, social media have propagated and amplified the belief that the small number of COVID-19 cases reported in March and April 2020 was an indication that SARS-CoV-2 cannot survive and spread in Sudan's sweltering heat. This belief mirrored similar misconceptions in other tropical regions, suggesting that high temperatures could kill the virus or reduce its spread. Another misconception is that prior exposure to malaria plasmodium or those with active malaria infections were at lower risk of SARS-CoV-2 infection or developing severe disease. This false perception led many individuals to reduce their adherence to public health measures. People delayed seeking medical care and neglected mask-wearing and social distancing, believing that malaria would offer sufficient protection.

This intersection of malaria and COVID-19 misinformation served as a key motivator for this research project, focusing on the clinical outcomes of co-infection. The aim is to explore how the simultaneous burden of malaria and COVID-19 influences disease progression, treatment responses, and recovery outcomes, addressing gaps in knowledge. It also seeks to challenge the misconception of malaria's protective role and highlights the need for integrated approaches to managing both diseases. Furthermore, this project underscores the importance of robust public health strategies based on evidence rather than assumptions, particularly in resource-constrained settings like Sudan. Accurate information and targeted interventions are crucial for ensuring that both malaria and COVID-19 are effectively managed, with minimal disruption to either disease's

control efforts. Additionally, the spread of misinformation about malaria's supposed protective effect against COVID-19 has indeed played a significant role in shaping the need for comprehensive research into the actual clinical outcomes of co-infection. Moreover, both infections place significant stress on the immune system, making patients more vulnerable to complications, including severe respiratory distress and multi-organ failure. This highlights the importance of managing both diseases concurrently, rather than relying on one to mitigate the other. This study ultimately seeks to fill the knowledge gap on the true impact of malaria-COVID-19 co-infections, dispelling dangerous myths, and guiding informed public health policies. However, despite the initially low COVID-19 cases during the early stages of the pandemic, the infection rate later rose rapidly. The case fatality ratio (CFR) of COVID-19 in Sudan reached 6.23%, with wide regional disparities, from 3.8% in Khartoum to as high as 30% and 66% in North and Central Darfur, respectively. These differences reflect disparities in hospital infrastructure and diagnostic facilities between the capital city (Khartoum) and the remote areas.[10,11] Additionally, the pandemic has severely impacted Sudan's healthcare system, with most public and private clinics forced to close due to high infection rates. COVID-19 isolation centers and intensive care services were overwhelmed by a lack of beds, oxygen supplies, and ventilators, further complicating the response to the pandemic.

1.1- Impact of the COVID-19 Pandemic on Malaria Control in Sudan:

Malaria, a mosquito-borne infectious disease, is caused by several types of plasmodium protozoa. The main species is plasmodium falciparum (PF), representing 87.6% of cases; it accounts for most of the morbidity and mortality, followed by plasmodium vivax (PV; 8.1% of cases) and PF/PV co-infections (5%).[12-15] According to the latest World Malaria report, there

were an estimated 249 million malaria cases in 85 malaria-endemic countries in 2022, a case incidence of 58 per 1000 population risk.

Over decades, malaria has been a constant scourge in Sudan, despite years of control efforts, it continues to be one of the leading infectious diseases that significantly impact the health system. Almost 75% of the population is at risk of infection and developing malaria. Malaria transmission is unstable putting the whole country at risk of malaria endemic. The incidence and transmission of malaria increases during times of heavy rain and floods, and whenever control activities are disrupted. In 2015, over 586 thousand confirmed malaria cases were reported by public health facilities; however, the estimated case count was 1.4 million. Likewise, 868 deaths from malaria were reported, the estimated number was 3,500. Malaria cases represent 8.7% and 12.2% of the total outpatient visits and hospital admissions, respectively. In 2015, the malaria CFR was 4.3%, making it a leading cause of death in Sudan[8].

Malaria control in Sudan during the COVID-19 pandemic faced several challenges, similar to those experienced in other malaria-endemic regions. The COVID-19 pandemic placed immense pressure on Sudan's healthcare system, diverting resources and attention away from malaria control efforts. Hospitals and clinics were often overwhelmed with COVID-19 cases, which affected the availability of services for malaria control, diagnosis, and treatment.

Here are some key points regarding malaria prevention/control during the pandemic period in Sudan:

1.1.1. The disruption of health services: The pandemic led to interruptions in malaria prevention and treatment services, such as the distribution of insecticide-treated nets (ITNs) and indoor residual spraying (IRS), and access to antimalarial medications, particularly in rural and remote areas.

1.1.2. **Supply Chain Challenges:** Lockdowns and restrictions affected the supply chains for essential malaria control tools, leading to shortages of drugs, bed nets, rapid diagnostic test kits, and insecticide.

1.1.3. **Increased Vulnerability:** The economic impact of the pandemic exacerbated existing vulnerabilities in Sudan, where many communities faced food insecurity and faced challenges in accessing healthcare facilities.

1.1.4. **Adaptation of Strategies:** In response to the challenges, health authorities and organizations in Sudan adapted their strategies to continue malaria control services. This included integrating malaria services with COVID-19 response efforts, utilizing telehealth for consultations, and ensuring that essential malaria services remained operational while addressing the pandemic.

1.1.5. **Community Engagement:** Community health workers played a crucial role in maintaining awareness about malaria prevention and treatment during the pandemic. They helped disseminate information about both malaria and COVID-19, encouraging communities to seek care when needed.

1.1.6. **Data Monitoring:** The pandemic highlighted the importance of robust data collection and monitoring systems to track malaria cases and ensure that control measures are effectively implemented, even in the face of a global health crisis.

1.1.7. **Global Collaboration and International Support:** International organizations, governments, and nongovernmental organizations (NGOs) have worked together to maintain focus on malaria control, emphasizing the need for continued funding and support to prevent a resurgence of the disease. Furthermore, the WHO continued to provide support to Sudan for malaria control. This included funding, technical assistance, and resources to help mitigate the impact of the pandemic on malaria services.

In conclusion, while the COVID-19 pandemic posed significant challenges to malaria control in Sudan, efforts were made to adapt and maintain essential services. Continued focus on malaria prevention and treatment remains critical to prevent a resurgence of the disease in the post-pandemic period.

1.2- Malaria in vulnerable populations:

1.2.1- Malaria in Children:

Children under five years of age are indeed the most vulnerable group to malaria, and the disease poses significant health risks that can lead to severe morbidity and mortality.[15] This age group is particularly vulnerable due to several factors, including their developing immune systems and the high prevalence of malaria in their communities. The impact of malaria on young children can be explained in different ways:

1.2.1.1. The impact of malaria infection during pregnancy can lead to **low birth weight**, which is a critical risk factor for neonatal morbidity and mortality. Infants born with low birth weight are more susceptible to infections and have a higher likelihood of complications in the first month of life.

1.2.1.2. High mortality rates: Children under five are at the highest risk of severe malaria, which can lead to death if not treated promptly. The WHO estimates that malaria is responsible for a significant proportion of child deaths in endemic areas.

1.2.1.3. Severe Malaria Manifestations: Severe malaria can manifest as cerebral malaria, characterized by neurological symptoms such as seizures, altered consciousness, and coma. This form of malaria can progress rapidly and may lead to death within hours or days if not treated promptly.

1.2.1.4.Severe anemia as a consequence of repeated infections, children who experience repeated malaria infections are at a heightened risk of developing severe anemia.

1.2.1.5.Increased Susceptibility to Infections: Children who have experienced malaria infections may have weakened immune systems, making them more susceptible to other infectious diseases, which can compound health challenges.

Malaria in children under five years of age is a critical public health issue that requires urgent attention. By implementing effective prevention and treatment strategies, healthcare providers and communities can significantly reduce the burden of malaria in this vulnerable population. Addressing the challenges posed by malaria is essential for improving child health outcomes and achieving broader public health goals in malaria-endemic regions.

1.2.2-Malaria in Pregnancy:

Malaria in pregnancy (MIP) poses a significant public health challenge in Sudan where malaria is endemic, the burden of MIP is particularly high, necessitating targeted interventions to reduce transmission and protect pregnant women. The MIP contributes to maternal anemia, fetal loss, premature delivery, intrauterine growth retardation, and low birth weight. Pregnant women are particularly vulnerable to malaria due to physiological changes that occur during pregnancy, which can compromise their immune response[15,16]. The following points highlight the critical aspects of malaria in this vulnerable population:

1.2.2.1. Maternal Health Risks:

1.2.2.1.1 Increased morbidity and mortality: Plasmodium falciparum, the most dangerous malaria parasite, can sequester in the placenta, leading to severe complications. It is estimated that malaria may contribute to nearly one-

quarter of all maternal deaths, particularly affecting women during the first trimester when over 60% of infections occur.[15,16]

1.2.2.1.2 Maternal Anemia: Malaria can lead to significant anemia in pregnant women, which increases the risk of complications during childbirth and can adversely affect maternal health.

1.2.2.2. Fetal Health Risks:

1.2.2.2.1. Fetal Loss and Premature Delivery: Malaria infection during pregnancy is associated with an increased risk of miscarriage and premature birth, which can have devastating effects on both the mother and the newborn.

1.2.2.2.2. Intrauterine Growth Retardation (IUGR): The infection can hinder fetal growth, leading to low birth weight (LBW) and associated health complications for the infant.

Effective management of malaria in vulnerable population requires an integrated approach that includes preventive measures such as ITNs, intermittent preventive treatment (IPT) with antimalarial drugs, and access to prompt diagnosis and treatment. Ensuring that pregnant women have access to comprehensive antenatal care services that include malaria screening and treatment can help mitigate risks. Furthermore, raising awareness about the risks of malaria during pregnancy and the importance of preventive measures can empower women to take proactive steps to protect themselves.

1.3-Sudan Humanitarian Crisis:

On April 15th, 2023, violent clashes erupted between the Sudanese Armed Forces (SAF) and the paramilitary Rapid Support Forces (RSF) in Khartoum and other parts of Sudan, resulting

in the displacement of more than 12 million people, including 10 million internally displaced people (IDPs) places immense strain on public services, such as healthcare, water, sanitation, and food distribution systems. The influx of refugees into neighboring countries such as Chad, South Sudan, Egypt, and the Central African Republic, has further destabilized these fragile states worsening regional instability, creating additional burdens for fragile neighboring states, and affecting the provision of humanitarian aid. Sudan's healthcare system, already struggling and weakened before the conflict, is now overwhelmed by the outbreak of diseases such as cholera, measles, dengue fever, and malaria, further restricting and limiting access to essential healthcare services. Furthermore, the conflict has exacerbated Sudan's existing challenges, including political and economic instability, ongoing internal conflicts, and the effects of climate emergencies.[12]

The world's worst internal displacement crisis continues to escalate, with looming famine and disease adding to the havoc wrought by conflict. In addition, the Integrated Food Security Phase Classification (IPC) analysis Technical Working Group reveals how the country is on the brink of a famine crisis in sixteen (16) areas and clusters of IDPs and refugees characterized by extremely high acute food insecurity. Over half of the population (25.6 M people) is in high levels of acute food insecurity, with 755,000 people already in catastrophic conditions and fourteen (14) areas at risk of famine crisis between June and September 2024. Various and significant disease outbreaks have occurred across Sudan, including over 10,000 suspected cholera cases, approximately 5,000 occurrences of measles, about 8,000 dengue fever cases, and over 1.2 million clinical cases of malaria.[13] The convergence of malnutrition and disease accelerates mortality rates, particularly among vulnerable groups such as children and displaced populations.

This humanitarian crisis reveals a critical link between conflict, health, and societal collapse. Violent conflict not only disrupts healthcare access but also triggers disease outbreaks and creates long-term socioeconomic instability. The Sudan crisis illustrates how weakened healthcare capacities can magnify vulnerabilities in a population already facing multiple stressors, including armed conflict, food shortages, environmental stressors, and climate hazards.[13,14]

Understanding Sudan's recent situation is crucial for highlighting and emphasizing the need to address both immediate humanitarian needs and systemic vulnerabilities. The severity of this crisis also provides a foundation for assessing the effectiveness of response efforts and identifying areas that require further intervention. Addressing these interconnected challenges is essential to reducing suffering and preventing the further breakdown of public systems in Sudan.

Justification:

This research project was driven by widespread misinformation, including beliefs that high temperatures or prior malaria infections, whether recent or ongoing, could provide protection against COVID-19. These misconceptions, along with the lack of longitudinal studies on the impact of malaria on COVID-19 outcomes, motivated and underscored the need for this study to determine their relationship and to advance our understanding of the clinical course and outcome in patients with concurrent malaria and COVID-19. Additionally, the relatively low prevalence and mortality of COVID-19 in malaria-endemic countries, such as Sudan, raised questions about the potential influence of malaria on COVID-19 dynamics.

The intersection of these factors motivated us to explore the relationship between malaria and COVID-19 to advance our understanding of the clinical course and outcomes in patients with concurrent infections. By addressing these gaps, this study aims to provide valuable insights that can inform public health strategies and improve patient care in regions affected by both diseases.

3- Literature review

3.1- Trends of the Global Burden of Malaria

While progress has been made in reducing malaria cases and deaths in recent years, there are still many areas where the burden of the disease remains high. Factors such as climate change, drug resistance, and inadequate funding for prevention and treatment programs continue to pose challenges in the fight against malaria. Governments, organizations, and individuals need to continue working together to address these issues and reduce the burden of malaria worldwide.

In 2019, Africa accounted for 94% (213 million cases) of malaria cases and 94% (386,000 deaths) of malaria deaths globally,[10] the majority of which appeared in the sub-Saharan African region[11]. According to the latest WHO's 2023 World Malaria report, the estimated number of global malaria cases in 2022 exceeded pre-COVID-19 pandemic levels in 2019[16].

The annual assessment and report noted that an estimated 249 million cases of malaria occurred in 85 malaria-endemic countries in 2022, a case incidence of 58 per 1000 population risk. For comparison, in 2019 there were an estimated 233 million global cases, a case incidence of 57 per 1000 population at risk. The numbers for 2022 were 55% higher than they should have been if the 2025 Global technical strategy for malaria targets are to be met—an incidence of only 26 cases per 1000 population at risk was expected in 2022[16].

3.2-The syndemic of COVID-19 and malaria in Africa:

The COVID-19 pandemic continues to wreak havoc around the world, particularly in resource-limited settings, the syndemic of COVID-19 and malaria in Africa presents a complex and challenging situation for public health systems in the region. Both diseases pose significant threats to the population, with overlapping risk factors and potential for co-infection. The impact

of the COVID-19 pandemic on malaria control efforts, such as disruptions to healthcare services and supply chains, has the potential to exacerbate the burden of malaria in Africa. Additionally, malaria is a mosquito-borne infectious disease caused by Plasmodium parasites, whose transmission depends on various impact factors, including but not limited to; climate changes, human behaviors, and the impact of socio-economic status[18-25].

Understanding the differences in transmission and clinical presentation of COVID-19 and malaria is important for effectively preventing, diagnosing, and management of both diseases. Public health measures tailored to the specific modes of transmission of each disease are essential in controlling their spread and reducing their impact on global health.

It is crucial for governments, healthcare providers, and international organizations to implement strategies that address the dual challenges of COVID-19 and malaria in a coordinated and comprehensive manner. This may include ensuring access to essential healthcare services, promoting preventive measures such as vector control and vaccination, and strengthening health systems to respond to both diseases effectively. Collaboration and innovation will be key in mitigating the syndemic of COVID-19 and malaria in Africa and protecting the health and well-being of the population.

3.3-The similarity between malaria and COVID-19:

While COVID-19 and malaria are caused by different pathogens and have distinct modes of transmission, there are some similarities in their clinical presentation and impact on public health. Malaria and COVID-19 share several clinical signs and symptoms such as myalgia, fever, cough, diarrhea, vomiting, headache, and fatigue. It can be challenging to distinguish COVID-19 from malaria, especially in areas where malaria is endemic. Additionally, the effect of malaria and COVID-19 on the coagulation system is an area of ongoing research and study.

Both diseases have been associated with abnormalities in the coagulation system, leading to an increased risk of blood clotting disorders and other complications.

The contemporaneity of the COVID-19 pandemic and malaria epidemics can be devastating in resource-limited settings, leading to overburdening of healthcare services and deterioration of resource scarcity.

3.4-The low prevalence of COVID-19 in malaria-endemic countries

Fighting COVID-19 in regions where malaria is endemic has been affected by ecological studies suggesting that countries with high malaria incidence tend to have lower COVID-19 mortality and by cross-sectional analyses reporting that patients previously exposed to malaria may have a better prognosis[4,5], based on the hypothesis that immunological memory against Plasmodium falciparum may mitigate SARS-CoV-2 infection[6,7]. Also, the suggestion that hydroxychloroquine (HCQ) and chloroquine (CQ) anti-malarial drugs, could be effective against SARS-CoV-2 has supported the notion that patients with SARS-CoV-2 previously exposed to malaria may have better outcomes[8, 10].

The use of hydroxychloroquine and chloroquine in the treatment of COVID-19 has been a topic of debate and ongoing research. Initially, there was interest in these drugs due to their potential antiviral properties and their ability to modulate the immune response. However, subsequent studies and clinical trials have shown mixed results regarding their effectiveness in treating COVID-19. A meta-analysis combining six studies showed no statistical significance in achieving virological cure and a decrease in time for clinical recovery in patients treated with HCQ or chloroquine[26]. Furthermore, another clinical trial reported that HCQ or CQ use in COVID-19 carries more risks than benefits[27].

Healthcare providers need to stay informed about the latest research and recommendations regarding the use of HCQ or CQ in COVID-19 treatment. Patients should consult with their healthcare provider before starting any new treatment and follow evidence-based guidelines to ensure safe and effective care.

3.5-Implementation of the RTS, S/AS01 malaria vaccine in sub-Saharan African countries

The first malaria vaccine, RTS,S, was recommended by WHO to prevent malaria in children in October 2021. The vaccine has reached nearly 2 million children in Ghana, Kenya, and Malawi through the Malaria Vaccine Implementation Program (MVIP) since 2019. RTS,S/AS01 (RTS,S) is a recombinant protein malaria vaccine that targets the circumsporozoite protein of PF, expressed by the malaria parasite at the pre-erythrocytic stage, in which part of the circumsporozoite sequence is coexpressed with fused and free hepatitis B surface antigen and formulated with the AS01 adjuvant[28,29].

The RTS,S vaccine has been shown to be safe and effective, resulting in a drop of 13% in all-cause early childhood deaths and a substantial reduction in severe malaria. Furthermore, the RTS,S vaccine is reaching children who are not using other forms of malaria prevention[30-33]. To date, at least 28 countries in the WHO African Region have expressed interest in introducing the malaria vaccine including Sudan.

In October 2023, WHO recommended a second safe and effective malaria vaccine, R21. The two vaccines will give broad coverage to children living in areas where malaria is a public health problem.

3.6-COVID-19 Vaccines

There are many COVID-19 vaccines shown to be safe and very effective at protecting people from severe COVID-19 illness, hospitalization, and death. The COVID-19 vaccines may also prevent the spread of disease to others. People who have already had COVID-19 should be

vaccinated to prevent getting COVID-19 again. COVID-19 vaccination can have a substantial impact on mitigating COVID-19 outbreaks. However, continued compliance with non-pharmaceutical interventions and protections is essential to achieve this impact.

According to the WHO, the date of the first COVID-19 vaccine introduction was 22 July 2020, since that time, more than 13.64 bn (Sudan accounts13.4 m) total COVID-19 vaccine doses has been administered, 67% of total population vaccinated with a complete primary series of a COVID-19 vaccine, 32% of total population vaccinated with at least one booster dose of a COVID-19 vaccine.

In African regions, a total of 646.45m COVID-19 vaccine doses has been administered since the date of the first COVID-19 vaccine introduction on January 10th, 2021. A 33% of total population vaccinated with a complete primary series of a COVID-19 vaccine, and only 6% of total population is vaccinated with at least one booster dose of a COVID-19 vaccine.

In Sudan, the first COVID-19 vaccine introduction was on March 9th, 2021. A total of 28.66m COVID-19 vaccine doses has been administered. 33% of the total population vaccinated with a complete primary series of a COVID-19 vaccine. Data not available for a percentage of total population vaccinated with at least one booster dose of a COVID-19 vaccine[35].

3.7-Vaccine Hesitancy and Lack of Awareness:

Vaccine hesitancy refers to a delay in acceptance or refusal of vaccines despite the availability of vaccination services. During the Pandemic, several millions worldwide, particularly in Africa, were hesitant to receive the COVID-19 vaccine. Vaccine hesitancy is not limited to COVID-19 vaccines and decisions related to other vaccination will also be affected.

The impact of social media on COVID-19 vaccine hesitancy in Africa can be significant. Social media platforms can amplify misinformation and conspiracy theories about vaccines, leading to

increased hesitancy among individuals. False information spread through social media can erode trust in vaccines, public health authorities, and the healthcare system as a whole[35-37].

Addressing vaccine hesitancy in Africa is crucial for achieving widespread vaccination coverage and controlling the spread of both COVID-19 and Malaria on the continent.

Much misinformation spread via social media said that the COVID-19 vaccine was introduced to kill the population and decrease the number of populations worldwide. Moreover, the vaccine can cause serious complications including infertility and cardiac diseases!

It is essential for public health organizations and governments to actively combat misinformation on social media and promote accurate information about all types of vaccines to address vaccine hesitancy effectively.

3.8-Social Stigma During COVID-19:

Stigmatization refers to the social process of labeling, stereotyping, and discriminating against individuals or groups based on certain characteristics, attributes, or behaviors that are perceived as deviant, undesirable, or different from the norm. Stigmatization can lead to negative attitudes, prejudice, and discrimination towards those who are stigmatized, resulting in social exclusion, marginalization, and harm to their well-being and dignity.

In Sudan, stigmatization was reported throughout the COVID-19 pandemic for COVID-19 patients and close contacts. Economic crisis, high poverty rate, food insecurity affects most of Sudan's population. Approximately, one-third of Sudan's population (36.1%) falls below the poverty line[39]. The lockdown during the pandemic has been hard for many peoples in Sudan, particularly for individuals who depend on a day-by-day income.

The lockdown during the pandemic had adversely affected the majority of Sudanese peoples in terms of social, mental health, and economic well-being.

4-Objectives:

4.1- Primary Objective:

The main objective of studying the syndemic of malaria and COVID-19 is to understand and investigate the impact of co-infection of COVID-19 with malaria on disease severity and clinical outcomes.

4.2- Secondary Objective:

i. Identify populations at increased risk of co-infection or severe outcomes from malaria and COVID-19, such as comorbidities, outcomes of both diseases among different demographic groups.

ii. Investigate the interactions between malaria and COVID-19, such as the potential for co-infection and the impact of one disease on the severity and outcomes of the other.

5- Material and Methods

5.1- Ethics statement

The study proposal was submitted to the Research Administration at the State Ministry of Health (MOH), Khartoum. An expedited review was conducted by the MOH Ethics Review Committees and approval was granted (**protocol COVID-19/001/2020**).

5.2- Study design and setting

Sudan is the third-largest African country and the seventeenth-largest in the world. The total land area is 1,765,048 Km2 (681,489 sq. miles).[1] The country has a total population of 43,849,260 and is located in the northeastern part of Africa. It shares borders with seven countries: the Central African Republic, Chad, Egypt, Eritrea, Ethiopia, Libya, and South Sudan. Positioned at the crossroads between Sub-Saharan Africa and the Middle East, Sudan also faces the Red Sea along its northeastern border.[40]

Khartoum State is where the national capital of Sudan, Khartoum city, is located. It is the most populous in Sudan, with an estimated population of 9.4 million people despite being the smallest state by area. Furthermore, Khartoum hosts the country's largest number of refugees and asylum seekers, an estimated over 309,000 people (38% of all the refugees in Sudan). An estimated 120,000 South Sudanese, 93,000 Syrian and 2,000 Yemeni refugees live in Khartoum. In addition to refugees from Eritrea, Ethiopia, the Central African Republic (CAR) and Chad.[41]

Khartoum is Sudan’s primary healthcare hub, but the system is severely stressed due to the combined effects of ongoing conflict and an overburdened infrastructure. These challenges are compounded by the influx of refugees, growing healthcare needs, and the fallout from wars,

which have resulted in severe shortages of supplies, staff, and functioning medical facilities. While Khartoum's hospitals have been central to the country's healthcare delivery, the system has struggled to respond to crises like COVID-19 and more recent conflicts, leaving many vulnerable populations without adequate care.

During the pandemic in Sudan, the healthcare systems, including referral and treatment pathways, underwent significant restructuring to handle the surge of cases. The pandemic highlighted the importance of coordination between healthcare providers among different healthcare facilities.

In particular, the MOH played a crucial role in establishing COVID-19 referral and treatment facilities. The MOH managed the temporary biggest and largest COVID-19 treatment center in Sudan, the Universal COVID-19 Treatment Center (UCTC). The UCTC had over 500 beds with central oxygen supply including fully equipped ICU/HDU beds, and 40 hemodialysis machines dedicated solely to COVID-19 patients experiencing kidney complications. Furthermore, specialized air filtration systems were installed to enhance infection control and reduce transmission risks within the facility. Additionally, UCTC was part of an integrated referral system that ensured patients with severe conditions were transferred from other healthcare facilities for advanced treatment. The referral system was coordinated through emergency response hotlines, allowing suspected COVID-19 patients to be directed to appropriate facilities using centralized triage and ambulance services. Additionally, ambulance services were mobilized to transfer severe cases from primary health facilities or community settings to designated COVID-19 hospitals and isolation centers according to disease severity.

Key Components of the COVID-19 Referral System in Khartoum:

During the COVID-19 pandemic, Sudan, implemented a referral system was developed to manage the influx of cases by streamlining efficient triage and delivering care at various levels. The system involved several layers to ensure that patients received appropriate care based on the severity of their symptoms:

1. **Triage and Screening Points**: These were set up at all healthcare facilities to quickly identify cases and assess their disease severity before referring them to isolation or treatment centers.
2. **Isolation of Mild Cases:** Home isolation was recommended for asymptomatic or mild cases, reducing the burden on hospitals. Moreover, specific isolation centers were designated for those who could not isolate at home, ensuring better control over community transmission.
3. **Treatment centers for Critical Cases:** Patients with critical conditions were prioritized for referral to specialized units. Referral coordination ensured patients were sent to facilities equipped with ventilators and HDU/ICU.

This coordination minimized delays and improved the efficiency of care delivery, especially for patients needing advanced support, such as mechanical ventilation.

The MOH worked to educate communities about the referral process and services. This included promoting early identification of symptoms and using the national COVID-19 hotline for advice and referral recommendations. Despite the huge efforts made by MOH and local communities, many challenges faced by the referral system such as limited healthcare infrastructure, shortages of medical supplies and trained staff, overwhelmed treatment centers, access issues, and resource limitations.

5.3 Study Participants

We report the results of a retrospective cohort study that assessed prospectively collected data. The study questions were formulated prior to data collection. We reviewed records of all patients who were admitted between May and December 2020 to the Universal COVID-19 Treatment Center (UCTC), Khartoum, Sudan. UCTC is the largest COVID-19 clinic in Sudan. It receives only critically ill patients from hospitals located in Khartoum state and beyond, primary isolation centers, and home isolation. All admitted patients had either COVID-19 confirmed by RT-PCR or suspected by clinical presentation and chest computer tomography. On admission, all patients without previously confirmed COVID-19 were tested by SARS-CoV-2 RT-PCR from nasopharyngeal and/or oropharyngeal swabs.

Malaria infection was screened by both an antigen-based rapid diagnostic test (RDT) and microscopic confirmation of Plasmodium falciparum (PF) and/or Plasmodium vivax (PV).

The Ecotest Malaria PF/Pan Rapid Test Device (MAL-W23M, CTK Biotech, Poway, CA, USA) is a chromatographic immunoassay for rapid qualitative determination of antigen in whole blood. This test depends on the presence of PF histidine-rich protein II specific to PF and plasmodium lactate dehydrogenase specific to PV in human blood samples; it has been applied with thin or thick microscopy on clinical samples. The results showed sensitivity and specificity of 99.9% and over 99%, respectively, relative to microscopy. All RDTs were maintained at room temperature until first use. RDTs were labelled with a sample identification number and the date on which the test was performed. Tests were conducted per manufacturer's instructions. All patients with confirmed COVID-19 who were tested for malaria were included in this study. Patients who were diagnosed with malaria before admission (n ¼ 13), were re-tested using RDT

and microscopy. Per our laboratory's experience, the Ecotest is accurate and performs well even in low parasite density.

Demographic, clinical, laboratory, and outcome data (Table 1) were extracted from the medical records and entered into an electronic, study-specific database. Steps to ensure data integrity and privacy were implemented.

5.4- Exposure:

The primary exposure was coinfection with malaria and SARSCoV-2, as defined above. In additional exploratory analyses, exposures were infection by various malaria species, namely PF, PV, and infection with both PF and PV. Malaria case severity was classified according to the World Health Organization (WHO) criteria (Table 2) [11].

5.5- Outcomes

5.5.1-Primary outcome:

The primary outcome was the all-cause in-hospital mortality. Time-at-risk started at hospital admission and ended either at the date of death or hospital discharge. As sensitivity analysis, start time at risk was changed to the onset of COVID-19 symptoms.

5.5.2-Exploratory outcomes:

Exploratory outcomes were the intensive care unit (ICU) admission, need for mechanical ventilation, acute kidney injury (AKI), and kidney replacement therapy (Fig. 3). AKI was defined per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[12]

6- Statistical analysis:

Continuous data are summarized as mean and standard deviation (SD) or as median and interquartile range (IQR). Differences between continuous variables are estimated by student's

t-test or Wilcoxon test. Categorical variables are summarized as proportions. Differences across groups are estimated using c2 or Fisher's exact tests. Event rates are calculated as incident rates per 1000 person-days of follow-up. Kaplan Meier survival curves are compared using the log-rank test. CI are reported with 95% confidence level.

For the primary outcome, all-cause in-hospital mortality, proportional hazard Cox models are built with malaria status as the main exposure. Models are built stepwise with incremental covariate adjustments made according to a priori selected variables based on causal assumptions between the exposure and the outcome. Accordingly, the first adjustment set includes age and sex: further adjusted models include cardiovascular comorbidities, diabetes, and hypertension as covariates.

We use generalized estimating equations with independent working covariance structure to estimate the associations between malaria on survival. Generalized estimating equations models are used to estimate population average effects in the presence of correlations between analysis units. In this study, we use geographical location as a cluster.

Proportional hazards assumptions are tested by inspection of Kaplan-Meier curves and testing log(time) interaction with malaria status. Effect modification of the Khartoum region on the malaria exposure is tested by including an interaction term between region and malaria in the fully adjusted model. Additionally, effect modification by age is tested by an interaction term between median age and malaria in the fully adjusted model. Missingness is assumed to be completely at random and a complete case analysis is performed. Secondary outcomes are modelled using logistic regression.

Adjusted ORs are estimated in models including age, sex, hypertension, diabetes, and cardiovascular diseases as covariates. Sensitivity analysis according to malaria severity is performed.

All analyses are performed using R software 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.Rproject.org/).

7- Results:

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

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Original article

Impact of COVID-19 and malaria coinfection on clinical outcomes: a retrospective cohort study

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ABSTRACT

Objectives: Despite the possibility of concurrent infection with COVID-19 and malaria, little is known about the clinical course of coinfected patients. We analysed the clinical outcomes of patients with concurrent COVID-19 and malaria infection.

Methods: We conducted a retrospective cohort study that assessed prospectively collected data of all patients who were admitted between May and December 2020 to the Universal COVID-19 treatment center (UCTC), Khartoum, Sudan. UCTC compiled demographic, clinical, laboratory (including testing for malaria), and outcome data in all patients with confirmed COVID-19 hospitalized at that clinic. The primary outcome was all-cause mortality during the hospital stay. We built proportional hazard Cox models with malaria status as the main exposure and stepwise adjustment for age, sex, cardiovascular comorbidities, diabetes, and hypertension.

Results: We included 591 patients with confirmed COVID-19 diagnosis who were also tested for malaria. Mean (SD) age was 58 (16.2) years, 446/591 (75.5%) were males. Malaria was diagnosed in 270/591 (45.7%) patients. Most malaria patients were infected by *Plasmodium falciparum* (140/270; 51.9%), while 121/270 (44.8%) were coinfected with *Plasmodium falciparum* and *Plasmodium vivax*. Median follow-up was 29 days. Crude mortality rates were 10.71 and 5.87 per 1000 person-days for patients with and without concurrent malaria, respectively. In the fully adjusted Cox model, patients with concurrent malaria and COVID-19 had a greater mortality risk (hazard ratio 1.43, 95% confidence interval 1.21–1.69).

Discussion: Coinfection with COVID-19 and malaria is associated with increased all-cause in-hospital mortality compared to monoinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **Rasha Hussein, Clin Microbiol Infect 2022;28:1152.e1–1152.e6**

Introduction

The COVID-19 pandemic disproportionally affects low- and middle-income countries [1,2]. In Sudan, a Sub-Saharan low- and middle-income country, poor healthcare literacy and the spread of false information further compound the impact of COVID-19 [3]. Fighting COVID-19 in regions where malaria is endemic has been affected by ecological studies suggesting that countries with higher malaria incidence tend to have lower COVID-19 mortality and by cross-sectional analyses reporting that patients previously exposed to malaria may have a better prognosis [4,5], based on the hypothesis that immunological memory against *Plasmodium falciparum* may mitigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [6,7]. Also, the suggestion that hydroxychloroquine, an anti-malarial drug, could be effective against SARS-

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CoV-2 has supported the notion that patients with SARS-CoV-2 previously exposed to malaria may have better outcomes [8–10].

Nevertheless, the impact of malaria on COVID-19 clinical outcomes remained unaddressed by longitudinal studies [10]. We therefore explored the impact of malaria coinfection on all-cause in-hospital mortality among patients with severe COVID-19.

Methods

Study design, setting, and participants

We report results of a retrospective cohort study that assessed prospectively collected data. The study questions were formulated prior to data collection. We reviewed records of all patients who were admitted between May and December 2020 to the Universal COVID-19 Treatment Center (UCTC), Khartoum, Sudan. UCTC is the largest COVID-19 clinic in Sudan. It receives only critically-ill patients from hospitals located in Khartoum state and beyond, primary isolation centers, and home isolation. All admitted patients had either COVID-19 confirmed by RT-PCR or suspected by clinical presentation and chest computer tomography. On admission, all patients without previously confirmed COVID-19 were tested by SARS-CoV-2 RT-PCR from nasopharyngeal and/or oropharyngeal swabs.

Malaria infection was screened by both an antigen-based rapid diagnostic test (RDT) and microscopic confirmation of *Plasmodium falciparum (PF)* and/or *Plasmodium vivax (PV)*.

The Ecotest Malaria PF/Pan Rapid Test Device (MAL-W23M, CTK Biotech, Poway, CA, USA) is a chromatographic immunoassay for rapid qualitative determination of antigen in whole blood. This test depends on the presence of *PF* histidine-rich protein II specific to *PF* and plasmodium lactate dehydrogenase specific to *PV* in human blood sample; it has been applied with thin or thick microscopy on clinical samples. The results showed sensitivity and specificity of 99.9% and over 99%, respectively, relative to microscopy. All RDTs were maintained at room temperature until first use. RDTs were labelled with a sample identification number and the date on which the test was performed. Tests were conducted per manufacturer's instructions.

All patients with confirmed COVID-19 who were tested for malaria were included in this study. Patients who were diagnosed with malaria before admission ($n = 13$), were re-tested using RDT and microscopy. Per our laboratory's experience, the Ecotest is accurate and performs well even in low parasite density.

Demographic, clinical, laboratory, and outcome data were extracted from the medical records and entered into an electronic, study-specific database. Steps to ensure data integrity and privacy were implemented.

Ethics statement

The study proposal was submitted to the Research Administration at the State Ministry of Health (MOH), Khartoum. Expedited review was conducted by the MOH Ethics Review Committees and approval was granted (protocol COVID-19/001/2020).

Exposure

The primary exposure was coinfection with malaria and SARS-CoV-2, as defined above. In additional exploratory analyses, exposures were infection by various malaria species, namely *PF*, *PV*, and infection with both *PF* and *PV*. Malaria case severity was classified according to the World Health Organization (WHO) criteria (Table S1) [11].

Outcomes

Primary outcome

The primary outcome was the all-cause in-hospital mortality. Time-at-risk started at hospital admission and ended either at the date of death or hospital discharge. As sensitivity analysis, start time at risk was changed to the onset of COVID-19 symptoms.

Exploratory outcomes

Exploratory outcomes were the intensive care unit/ICU admission, need for mechanical ventilation, acute kidney injury (AKI), and kidney replacement therapy. AKI was defined per Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [12].

Statistical analysis

Continuous data are summarized as mean and standard deviation (SD) or as median and interquartile range (IQR). Differences between continuous variables are estimated by student's t-test or Wilcoxon test. Categorical variables are summarized as proportions. Differences across groups are estimated using χ^2 or Fisher's exact tests. Event rates are calculated as incident rates per 1000 person-days of follow-up. Kaplan Meier survival curves are compared using the log-rank test. CI are reported with 95% confidence level.

For the primary outcome, all-cause in-hospital mortality, proportional hazard Cox models are built with malaria status as the main exposure. Models are built stepwise with incremental covariate adjustments made according to *a priori* selected variables based on causal assumptions between the exposure and the outcome. Accordingly, the first adjustment set includes age and sex; further adjusted models include cardiovascular comorbidities, diabetes, and hypertension as covariates.

We use generalized estimating equations with independence working covariance structure to estimate the associations between malaria on survival. Generalized estimating equations models are used to estimate population average effects in the presence of correlations between analysis units. In this study, we use geographical location as the cluster.

Proportional hazards assumptions are tested by inspection of Kaplan-Meier curves and testing log(time) interaction with malaria status. Effect modification of the Khartoum region on the malaria exposure is tested by including an interaction term between region and malaria in the fully adjusted model. Additionally, effect modification by age is tested by an interaction term between median age and malaria in the fully adjusted model. Missingness is assumed to be completely at random and a complete case analysis is performed.

Secondary outcomes are modelled using logistic regression. Adjusted ORs are estimated in models including age, sex, hypertension, diabetes, and cardiovascular diseases as covariates. Sensitivity analysis according to malaria severity is performed.

All analyses are performed using R software 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Between May and December 2020, 638 patients were admitted to UCTC in Khartoum, Sudan. Malaria testing was available in 591 (92.6%) patients, constituting the final analytical cohort. All 591

patients had confirmed COVID-19 (Fig. 1). Forty-seven patients without malaria testing were excluded from the analysis. Included and excluded patients showed mostly similar characteristics (Table S2). Patients from Khartoum and other regions had mostly comparable demographics, comorbidities, and COVID-19 symptoms at presentation (Table S3). Malaria was confirmed in 270/591 (45.7%) subjects, including 13 patients with diagnosis two to five days prior to admission; these patients showed no parasitemia when re-tested, probably due to previous anti-malarial treatment. Malaria treatment (usually artemether/lumefantrine 80/480 tablets) was instituted in most patients, including 39 patients with typical clinical manifestation yet absent positive tests. A greater proportion of malaria patients resided outside Khartoum (57.8%). Additionally, more males and diabetic patients were present in the malaria group. Most malaria patients were infected by *PF* (51.9%); 44.8% were coinfected with *PF* and *PV* (Table 1). Fever and tiredness were present in almost all patients in both groups, while cough tended to be more prevalent among individuals with malaria. A primary COVID-19 contact was more often identified among patients with malaria (13.9% vs. 26.8%).

Fig. S1 summarizes the process for case definition of severe malaria; 240/270 (88.9%) met the WHO criteria for severe malaria at clinical presentation (Table S4). Most patients with malaria had renal impairment, acidosis, prostration, and hyperparasitemia at clinical presentation (Table S4). More than one third presented with shock; lung edema was diagnosed in 14.6%. Compared to patients with non-severe malaria, severe patients tended to have more hypertension and diabetes, while presenting symptoms were not different other than those defined by the WHO criteria (Tables S4 and S5). More patients in the severe malaria group needed oxygen support (95%) as compared to non-severe malaria (91%) and to those without malaria diagnosis (89%). Oxygen flow rates were 11.3 (±4.6), 9.3 (±4.7), and 10.5 (±4.8) L/min for severe malaria, non-severe malaria, and non-malaria groups, respectively.

Median follow-up was 29 days. Crude mortality rates were 10.71 and 5.87 per 1000 person-days in the malaria and non-malaria groups, respectively (Fig. 2). Median length of hospital stay was 21 days (IQR: 14–28) for the malaria group and 20 days (IQR: 15–28) for the non-malaria group ($p = 0.49$; Wilcoxon test). The median period between symptom onset and hospital admission was 6 days (IQR: 5–9) in the malaria group and 8 days (IQR: 5–11) in the non-malaria group ($p = 0.005$; Wilcoxon test).

Table 2 displays the hazard ratios (HRs) for all-cause in-hospital mortality, the primary outcome, in models with stepwise adjustments for potential confounders. In general, individuals with malaria coinfection were at greater risk of mortality in both unadjusted and adjusted analyses (fully adjusted model: HR 1.43, 95% CI 1.21–1.69). Coinfection with *PF* ($n = 140$) was associated with an about 50% increased mortality (fully adjusted model: HR 1.45, 95% CI 1.11–1.85). The risk was comparable for a combined infection with *PF* and *PV* ($n = 121$; fully adjusted model: HR 1.39, 95% CI 0.95–2.01). Sole *PV* infection was rare ($n = 9$) and the CI around the HR point estimate wide (fully adjusted model: HR 2.12, 95% CI 0.78–5.72). No interaction was found between malaria diagnosis and residence geography ($p = 0.8$) or age ($p = 0.58$).

Fig. S2 depicts the survival curves stratified by malaria status and severity. Patients with severe malaria tended to have shorter survival than non-malaria and non-severe malaria groups, (log-rank test $p = 0.001$). Severe malaria patients, compared to individuals without malaria, had an increased adjusted risk for all-cause mortality (HR 1.51, 95% CI 1.24–1.84). The group with non-severe malaria, compared similarly, did not have an increase in mortality risk (HR 1.06, 95% CI 0.45–2.50), although CI are wide.

Fig. 3 describes the adjusted ORs estimates for exploratory outcomes. Individuals with malaria had a greater risk for all-cause in-hospital mortality (OR 2.12, 95% CI 1.39–3.25), ICU admission (OR 1.46, 95% CI 1.02–2.09), and AKI (OR 1.52, 95% CI 1.06–2.18). The need of kidney replacement therapy (OR 1.0, 95% CI 0.59–1.69) and mechanical ventilation support (OR 1.36, 95% CI 0.90–2.05) did not differ between groups.

Discussion

Principal findings

The main finding of our study is the increased all-cause in-hospital mortality in critically-ill patients coinfected with SARS-CoV-2 and malaria treated in a tertiary COVID-19 referral center in Khartoum, Sudan. Point estimates of HRs were consistent across distinct malaria species. Our exploratory analyses demonstrated that AKI and ICU admission were more common among coinfected patients. Noteworthy, the median period between symptom onset and hospital admission was two days shorter in the malaria group, possibly reflecting some societal stigmatization of COVID-19.

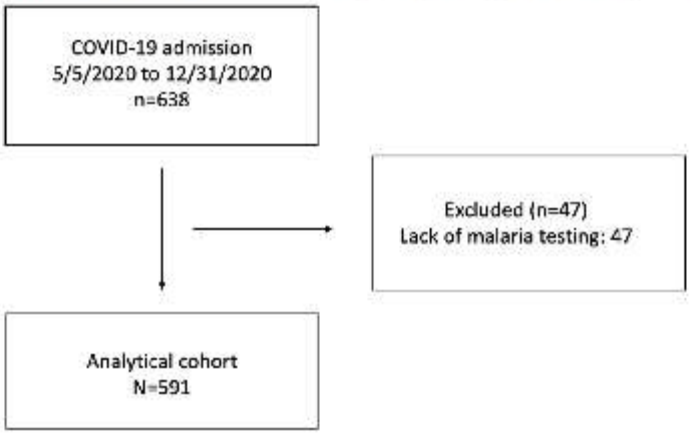

Fig. 1. Flow-chart of the selection process.

Table 1
Descriptive statistics of the study population

	Without malaria	With malaria
No. (% of total population)	321 (54.3)	270 (45.7)
Demographics No. (% of group)		
Age, years mean (SD)	58.5 (17.3)	57.3 (15.0)
Male	232 (72.3)	214 (79.3)
Sudanese nationality	309 (96.3)	261 (96.7)
Khartoum resident	226 (70.4)	156 (57.8)
Comorbidities No. found/No. available (% of available)		
Hypertension	60/263 (22.8)	55/247 (22.3)
Diabetes	102/320 (31.9)	111/270 (41.1)
Renal disease	25/321 (7.8)	22/270 (8.1)
Malignancy	23/321 (7.2)	8/270 (3.0)
HIV	7/321 (2.2)	0/270 (0.0)
Cardiovascular disease	57/320 (17.8)	41/269 (15.2)
Neurological Disease	19/320 (5.9)	23/270 (8.5)
Malaria species No. (% of group)		
Plasmodium falciparum	0 (0.0)	140 (51.9)
Plasmodium falciparum and *Plasmodium vivax*	0 (0.0)	121 (44.8)
Plasmodium vivax	0 (0.0)	9 (3.3)
COVID-19 symptoms No. found/No. available (% of available)		
Primary COVID-19 contact identified[a]	32/230 (13.9)	38/142 (26.8)
Fever	315/321 (98.1)	266/270 (98.5)
Cough	222/321 (69.2)	216/270 (80.0)
Tiredness	318/321 (99.1)	270/270 (100.0)
Chest pain	222/321 (69.2)	182/270 (67.4)

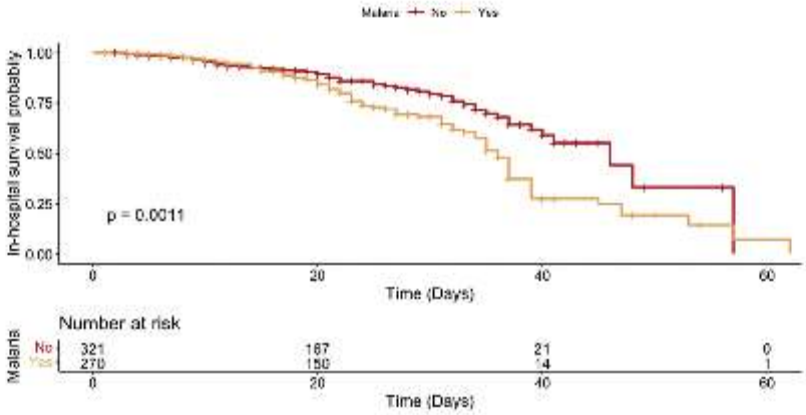

Fig. 2. Kaplan-Meier curves and number of patients at risk for all-cause in-hospital mortality.

Table 2
Hazard ratios for all-cause in-hospital mortality at different levels of adjustment

	No. (%)[a]	Hazard Ratios (95% CI)		
		Model 1	Model 2	Model 3[b]
Malaria status	270 (46)	1.74 (1.46–2.08)	1.75 (1.46–2.11)	1.43 (1.21–1.69)
Malaria species				
Plasmodium falciparum	140 (52)	1.71 (1.39–2.09)	1.73 (1.36–2.19)	1.45 (1.14–1.85)
Plasmodium vivax	9 (3.0)	2.03 (0.86–4.81)	1.95 (0.84–4.51)	2.12 (0.78–5.72)
Plasmodium falciparum and *Plasmodium vivax*	121 (45)	1.76 (1.34–2.30)	1.77 (1.27–2.47)	1.39 (0.95–2.01)

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: Model 2 plus hypertension, diabetes, and cardiovascular diseases.
[a] For malaria species, the denominator is 270 (number of malaria positive cases), whereas for malaria status it is the whole population (591).
[b] There were 23 missing data points (8.5%) for hypertension status among subject with malaria and 58 (18%) among non-malaria subjects. One patient in the non-malaria group (0.3%) had missing diabetes information.

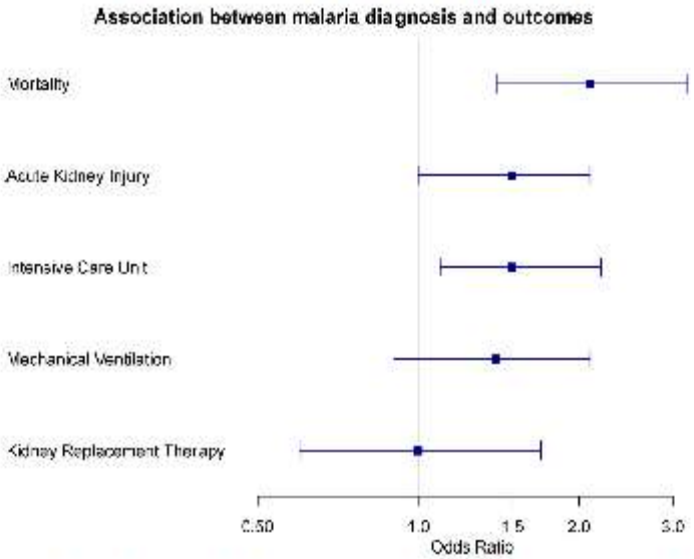

Fig. 3. Forrest plot. Adjusted odds ratios and 95% confidence intervals for the associations between malaria and adverse clinical outcomes. Models are adjusted for age, sex, hypertension, diabetes, and cardiovascular disorders as comorbidities.

Findings of the present study in light of previous publications

The impact of previous exposure to malaria on COVID-19 associated outcomes has been previously explored in heterogeneous settings with conflicting findings [10]. Early into the pandemic, ecological studies have suggested that countries where malaria is endemic tended to report lower SARS-CoV-2 infection rates and case fatality ratios [4,5]. These studies gave rise to claims of potential benefits of anti-malarial drugs (e.g. hydroxychloroquine) for COVID-19 treatment and prophylaxis. These claims have not been corroborated by subsequent randomized controlled trials [8,9]. Moreover, biological mechanisms by which immune response to previous malaria exposure could be protective against SARS-CoV-2 infection or severity were hypothesized, (e.g., a potential role of immunological memory against *Pf* as a mediator for lower risk of COVID-19 [7]). Findings from translational research suggested cross-immunity between *Plasmodium* species and SARS-CoV-2 as biologically plausible mechanisms, as epitope mapping confirmed common antigens between *Pf* and SARS-CoV-2 [6,13]. Another study suggested that malaria infection may lead to improved outcomes in patients with COVID-19, since SARS-CoV-2 clearance was faster in coinfected healthcare workers [14]. The clinical implications of these findings are uncertain and warrant longitudinal studies of clinical outcomes among coinfected subjects. A meta-analysis of observational data and case series indicated that patients previously exposed to malaria have more severe inflammation as indicated by C-reactive protein, procalcitonin, D-Dimer, and other inflammatory biomarkers; however, clinical outcomes have not been addressed [10]. The impact of coinfection on hematological and hepatic outcomes was reported in 12 patients with coinfection—hyperbilirubinemia and mild anemia were seen in four (33%) and two (17%) patients, respectively [10]. The rates of jaundice (2.1%) and severe anemia (3.8%) were lower in our cohort.

Strengths and limitations of the study

Our study has several strengths, first and foremost the availability of detailed health records and a well-organized, systematic, and robust testing strategy for both COVID-19 and malaria. Almost 93% of patients admitted to UCTC were tested for COVID-19 and malaria, mitigating bias by indication. In addition, the study population comprises patients from urban and rural areas. Exploring the impact of geography was motivated by well-known transportation and healthcare access challenges for patients residing outside Khartoum. We are not aware of data indicating a different epidemiological profile between Khartoum and other Sudanese cities regarding COVID-19 and malaria. Our analyses have some limitations. The observations come from a tertiary COVID-19 referral center and may not be generalizable to other care settings. The observational study design prevents us from excluding residual confounding. Additionally, we did not collect outcomes specific to COVID-19-associated complications, such as thrombotic events. We acknowledge that the influence of age and other comorbidities vs. malaria could be masked by the low proportion of young (<40 years), non-diabetic subjects. Lastly, we lack a quantitative measurement of *Plasmodium* parasitemia. Nevertheless, our findings are robust and add to the scarce literature on malaria and COVID-19 coinfection.

Implications for practice or policy and future research

Healthcare workers practicing in areas where malaria is endemic should always consider the possibility of coinfection with COVID-19 and malaria. Swift diagnosis is key, and we suggest a low threshold for malaria testing in patients with COVID-19 and residence in or recent travel to such areas. While we acknowledge limitations of using the WHO malaria severity classification in coinfected patients, our data show that applying these criteria may aid risk stratification

and prognostication. In patients with malaria, it is important to rapidly administer the regionally recommended anti-malarial regimen. As lung involvement can occur in both infections, we suggest computed tomography imaging of the lungs in coinfected patients to ascertain pulmonary pathologies [15]. If lung involvement is suggestive of COVID-19, specific therapeutic schemes (e.g. antivirals, monoclonal antibodies) should be considered, understanding that some therapeutics may be ineffective against specific SARS-CoV-2 variants and that there is no consensual evidence that a late administration of monoclonal antibodies or antivirals impacts outcome in hospitalized patients.

Our study challenges the notion that malaria mitigates the clinical course of COVID-19. We believe that specific care pathways for patients coinfected with COVID-19 and malaria are warranted. Importantly, national and international bodies should step up efforts to increase SARS-CoV-2 vaccination rates in areas where malaria is endemic. Future research into the clinical outcomes in non-hospitalized patients with malaria and COVID-19 coinfection is warranted to complement our findings.

Transparency declaration

PK is an employee of the Renal Research Institute, a wholly owned subsidiary of Fresenius Medical Care. PK receives author royalties from UpToDate and HSTalks and holds stock in Fresenius Medical Care. PK is on the Editorial Board of Blood Purification, Kidney and Blood Pressure Research, and Frontiers in Nephrology. PK is inventor on multiple patents in the field of kidney medicine.

RPF is employed by Arbor Research Collaborative for health, who runs the DOPPS studies. Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. Funding is provided to Arbor Research Collaborative for Health and not to RPF directly. For details see https://www.dopps.org/AboutUs/Support.aspx. RPF receives research grants from Fresenius Medical Care, National Council for Scientific and Technological Development, honoraria (paid to employer) from AstraZeneca, Boehringer-Lilly, Novo Nordisk, Akebia, Bayer for participation in advisory Boards and educational activities.

All other authors have declared no conflict of interest.

No external funding was received.

Ethics committee approval

The study proposal was submitted to the Research Administration at the State Ministry of Health (MOH), Khartoum. Expedited review was conducted by the MOH Ethics Review Committees and approval was granted (protocol COVID-19/001/2020).

Data sharing

The datasets used in the current study are available from the authors in an anonymized format upon reasonable request.

Author's contributions

Conceptualization: RH, RPF, PK; Data curation: RH; Formal analysis: MG, PK; Investigation: MG, PK; Methodology: RH, MG, RFP, PK; Project administration: RH, NI, MMA, AET, NA, HA; Software: RH, GM, NI, MMA, AET, NA, HA, PK; Supervision: RH, NA, HA; Validation: RH, NI, MMA, AET, NA, HA; Writing – original draft: RH, GM, RPF, PK; Writing – review & editing: all authors.

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This manuscript is part of a PhD thesis of RH, at the School of Medicine, Pontificia Universidade Católica do Paraná (PUCPR), Curitiba, Brazil. RH has been scientist-in-residence at the Renal Research Institute, New York, N; she is a mentee of PK as part of the International Society of Nephrology (ISN) Mentorship Program and the collaboration between Soba University Hospital and PUCPR has been supported by the ISN's Sister Renal Center.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.03.028.

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8- Conclusion

The impact of previous exposure to malaria on COVID-19 associated outcomes has been previously explored in heterogeneous settings with conflicting findings. Early into the pandemic, ecological studies have suggested that countries where malaria is endemic tended to report lower SARS-CoV-2 infection rates and case fatality ratios. These studies gave rise to claims of potential benefits of anti-malarial drugs (hydroxychloroquine) for COVID-19 treatment and prophylaxis. These claims have not been corroborated by subsequent randomized controlled trials. Moreover, biological mechanisms by which immune response to previous malaria exposure could be protective against SARS-CoV-2 infection or severity were hypothesized, (e.g., a potential role of immunological memory against PF as a mediator for lower risk of COVID-19. Findings from translational research suggested cross-immunity between Plasmodium species andSARS-CoV-2 as biologically plausible mechanisms, as epitope mapping confirmed common antigens between PF and SARS-CoV-2. Another study suggested that malaria infection may lead to improved outcomes in patients with COVID-19 since SARS-CoV-2 clearance was faster in coinfected healthcare workers. The clinical implications of these findings are uncertain and warrant longitudinal studies of clinical outcomes among coinfected patients. A meta-analysis of observational data and case series indicated that patients previously exposed to malaria have more severe inflammation as indicated by C-reactive protein, procalcitonin, D-Dimer, and other inflammatory biomarkers; however, clinical outcomes have not been addressed. The impact of coinfection on hematological and hepatic outcomes was reported in 12 patients with coinfection and hyperbilirubinemia, and mild anemia was observed in our (33%) and two (17%) patients, respectively. The rates of jaundice (2.1%) and severe anemia (3.8%) were lower in our cohort.

Healthcare workers practicing in areas where malaria is endemic should always consider the possibility of coinfection with COVID-19 and malaria. Swift diagnosis is key, and we suggest a low threshold for malaria testing in patients with COVID-19 and residence in or recent travel to such areas. While we acknowledge the limitations of using the WHO malaria severity classification in coinfected patients, our data shows that applying these criteria may aid risk stratification and prognostication. In patients with malaria, it is important to rapidly administer the recommended anti-malarial regimen. As lung involvement can occur in both infections, we suggest computed tomography imaging of the lungs in coinfected patients to ascertain pulmonary pathologies. If lung involvement is suggestive of COVID-19, specific therapeutic schemes (e.g. antivirals, monoclonal antibodies) should be considered, understanding that some therapeutics may be ineffective against specific SARS-CoV-2 variants and that there is no consensual evidence that late administration of monoclonal antibodies or antivirals impacts outcome in hospitalized patients. Our study challenges the notion that malaria mitigates the clinical course of COVID-19. We believe that specific care pathways for patients coinfected with COVID-19 and malaria are warranted. Importantly, national and international bodies should step up efforts to increase both SARS-CoV-2 and malaria vaccination rates in areas where malaria is endemic. Future research into the clinical outcomes in non-hospitalized patients with malaria and COVID-19 infection is warranted to complement our findings.

This study was conducted during the COVID-19 pandemic, prior to the outbreak of the recent conflict in Sudan. Although the conflict emerged after our study's completion, it has further disrupted healthcare systems, exacerbating and worsening pre-existing challenges such as disease outbreaks, food insecurity, and displacement. These disruptions highlight the

importance of understanding the burden of overlapping health crises, particularly in contexts where healthcare systems are under strain from multiple crises, such as Sudan

9- Final considerations

This thesis is the result of an international collaboration between Pontificia Universidade Católica do Parana (PUPCR), the International Society of Nephrology's Renal Sister Center (PUCPR, and the Sudanese Medical Association), which was active between 2014 and 2020, and the Renal Research Institute, USA, NY.

The study was done during the COVID-19 pandemic in a critical care setting in the biggest treatment center for critical patients who need ventilatory support and HDU/ICU admission. Given the similarities in symptoms between malaria and COVID-19, it's not surprising that many patients might have been administered antimalarial medications without proper medical consultation. Furthermore, the social stigmatization surrounding COVID-19 could have influenced treatment decisions, leading to a higher likelihood of misdiagnosis or inappropriate treatment. Testing all patients for malaria was a critical step, as it could clarify the impact of co-infection and guide more effective treatment protocols.

It is difficult to distinguish accurately between malaria and COVID-19 in malaria-endemic areas like Sudan since the two diseases share many manifestations. The distinction is important in clinical practice and epidemiology. Furthermore, understanding the differences between malaria infection and malaria disease is essential in malaria COVID-19 coinfection.

9.1. Malaria Infection Versus Disease

Malaria is used as a generic reference term to protozoa of the genus Plasmodium usually as part of the compound term **malaria parasites**. Malaria infection is the presence of the plasmodium parasite in the body which can or may not cause the disease, while malaria disease is the illness and clinical symptoms caused by the parasite which can range from mild to serious, life-threatening disease. The severity

of malaria depends mainly on the species of parasite and the person's immune status. The main difference between malaria infection and disease is that having the parasite doesn't necessarily mean having the disease. Additionally, in endemic areas, many people who are infected with plasmodium do not show any symptoms (asymptomatic carriers) they develop partial immunity over time, and they can transmit the parasite to mosquitoes, contributing to the spread of malaria to others.[45]

In countries with a high burden of malaria, patients with symptoms such as fever, fatigue, myalgia, headache, and acute respiratory distress, both malaria and COVID-19 tests should always be performed. Moreover, healthcare workers will face a great challenge in case of a syndemic due to mutual side effects and manifestations leading to worse outcomes. On the other hand, patients with malaria infection without malaria disease must receive antimalarial medications according to the protocol and guidelines to reduce the potential risk of transmission.

9.2. Healthcare Disruptions from Conflict

Sudan was not prepared to manage and control the pandemic's emergence. The country's health system was already fragile, characterized by limited infrastructure and a shortage of medical supplies and personnel. As healthcare resources were redirected towards combating COVID-19, efforts to control malaria faced significant setbacks, raising concerns about potential surges in malaria cases. Understanding the interplay between these two diseases is crucial for developing effective strategies to mitigate their impact and safeguard the health of vulnerable populations in Sudan. This situation underscores the need for integrated approaches to disease management and robust public health strategies that address multiple health challenges simultaneously.

Sudan faced significant challenges during the last decades and has been further strained by the recent conflict. The ongoing military conflict resulted in extensive damage to healthcare facilities, further limiting access to medical care and disrupting services for those in need.

The recent crisis led to mass internal displacement with many people fleeing to safer areas or crossing the borders of neighboring countries which complicate access to the health care facilities for displaced populations. Furthermore, the combination of COVID pandemic and recent military conflict has created a compounded humanitarian crisis which increases food insecurity, malnutrition, outbreaks of infectious diseases, and heightened health risks.

The United Nations High Commissioner for Refugees (UNHCR) is concerned for the health and protection of Sudanese refugees across Sudan's borders. The UNHCR highlights an increase of malaria cases in refugee sites, triggered by the onset of the heavy rainy season and floods, in addition alarming rates of malnutrition, measles, acute respiratory infections, acute watery diarrhea, and the risk of outbreaks of cholera. Risks are compounded by the water, sanitation, hygiene infrastructure, limited medical supplies, and health workers.[44]

The situation in Sudan remains critical, requiring urgent international attention and support to rebuild the health system and provide essential services to the population. While there are many international assistance, logistical challenges and exciting instability hindered effective implementation of response efforts. Access challenges have delayed the delivery of critical medicines and urgent supplies.

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Figure 1. Flow chart for malaria severity definition according to World Health Organization criteria.

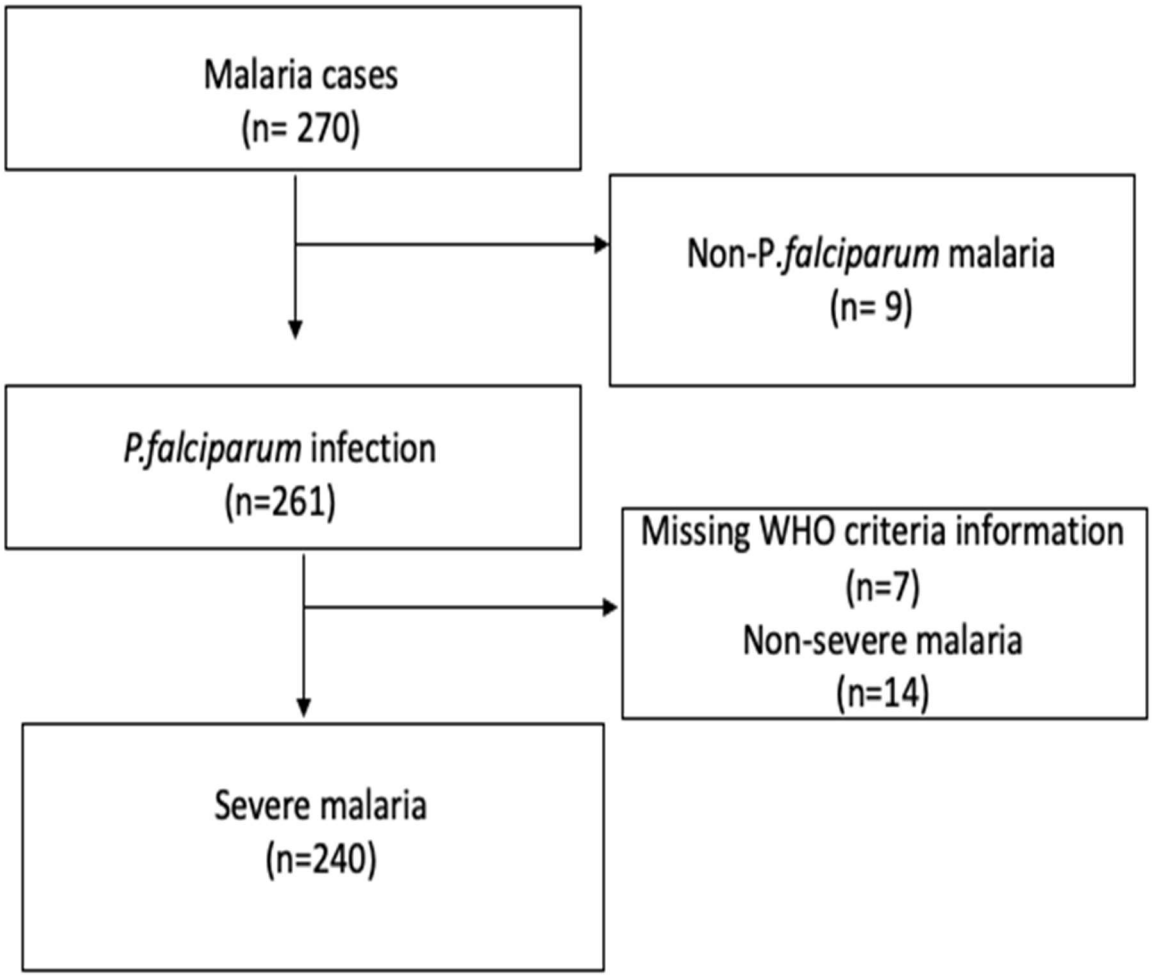


Figure 2. Kaplan-Meier curves and number of patients at risk for all-cause in-hospital mortality stratified for malaria severity.

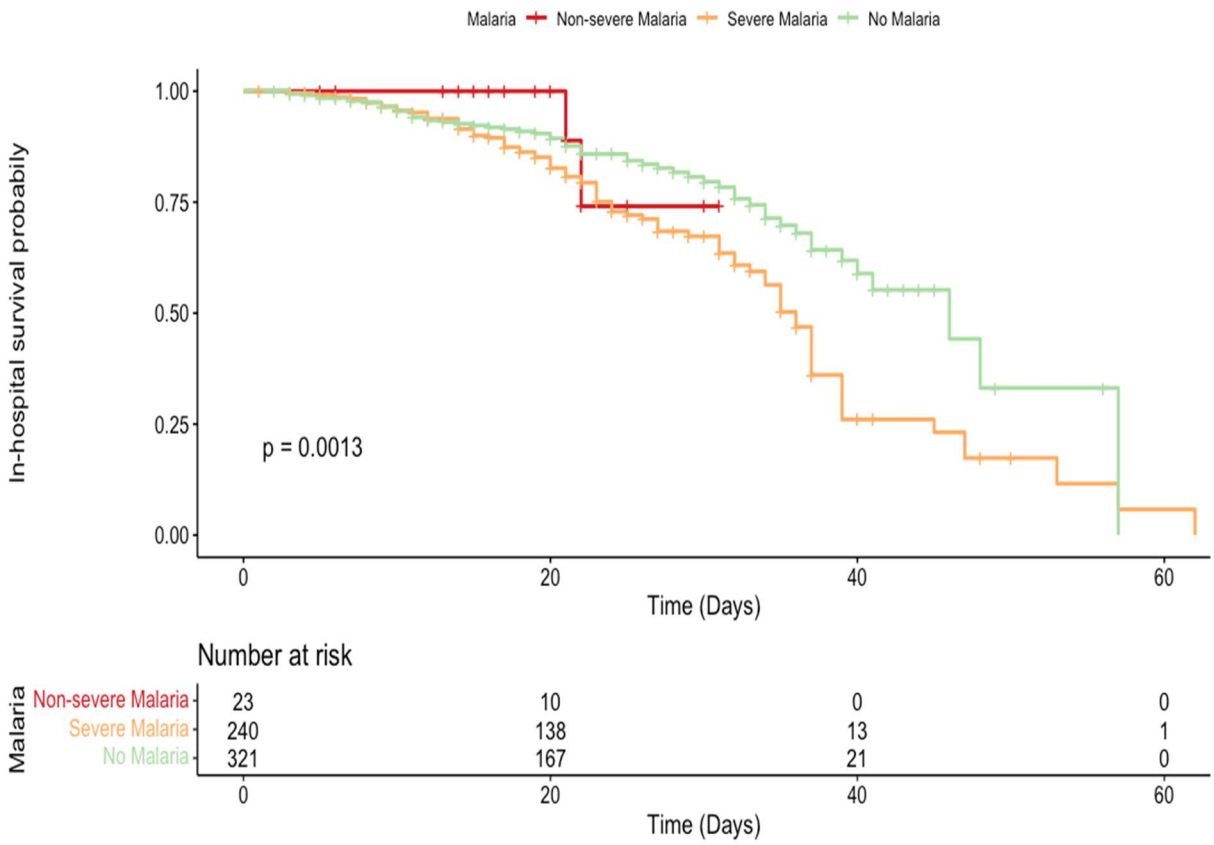


Figure 3: Forrest plot. Adjusted odds ratios and 95% confidence intervals for the associations between malaria and adverse clinical outcomes. Models are adjusted for age, gender and hypertension, diabetes, and cardiovascular disorders as comorbidities.

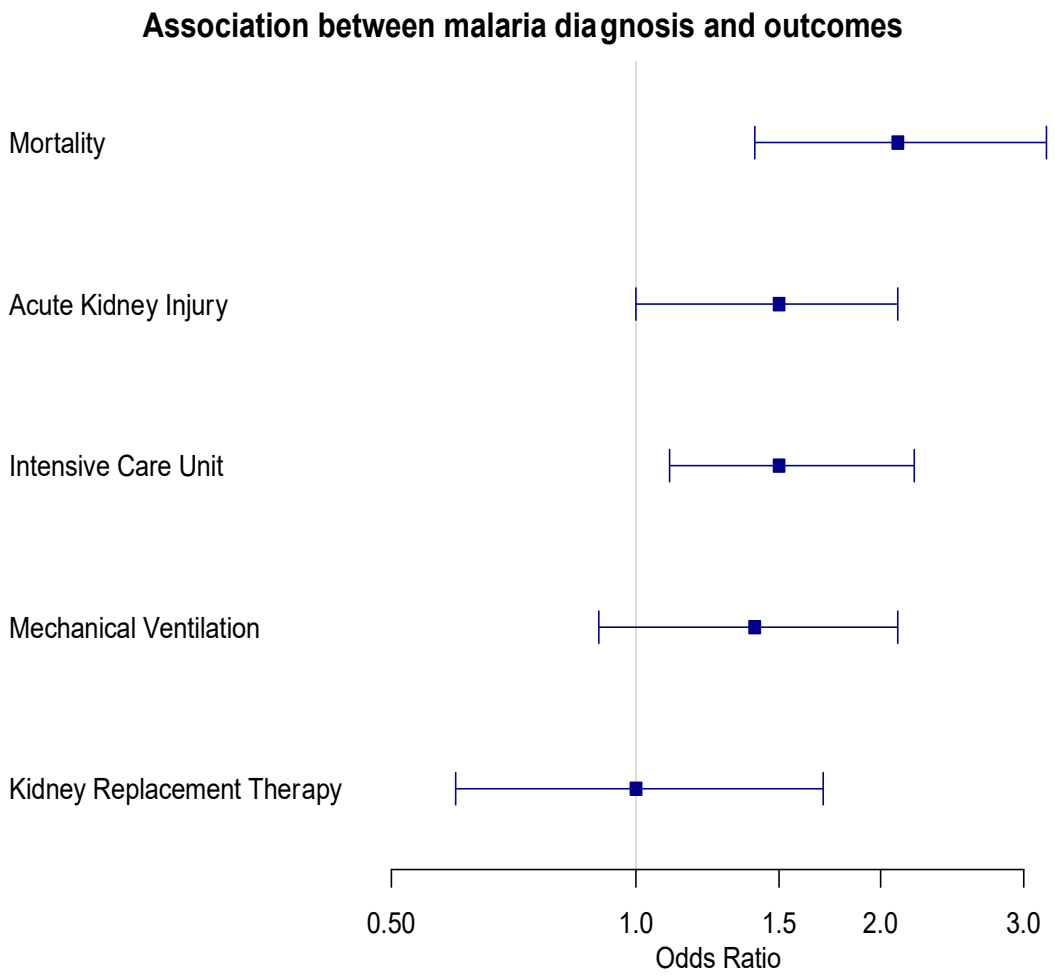


Table 1. Descriptive characteristics of included (N=591) and excluded (N=47) patients.

	Included	**Excluded***	**p-value**
N (% of total population)	**591(92.6)**	**47 (7.4)**	
Demographics N (% of group)			
Age (years); mean (SD)	**57.99 (16.33)**	**56.13 (15.89)**	**0.45**
Male	**446 (75.5)**	**36 (76.6)**	**1.00**
Sudanese nationality	**570 (96.4)**	**44 (93.6)**	**0.56**
Khartoum resident	**382 (64.6)**	**19 (40.4)**	**0.002**
Comorbidities **N found / N available (% of available)**			
Hypertension	**115 / 510 (22.5)**	**28 / 47 (59.6)**	**<0.001**
Diabetes	**213 / 590 (36.1)**	**12 / 47 (25.5)**	**0.19**
Renal disease	**47 / 591 (8.0)**	**0 /47 (0.0)**	**0.09**
Malignancy	**31 /590 (5.2)**	**5 / 47 (10.6)**	**0.23**
HIV	**7 / 591 (1.2)**	**0 / 47 (0.0)**	**0.98**
Cardiovascular disease	**98 / 590 (16.6)**	**7 / 47 (14.9)**	**0.92**
Neurological disease	**42 / 530 (7.9)**	**0 / 10 (0.0)**	**0.74**
Malaria status N (% of group)			-
Malaria positive	**321 (54.3)**	**missing**	
Plasmodium falciparum	**121 (20.5)**	**missing**	
Plasmodium falciparum **and** ***Plasmodium vivax***	**9 (1.5)**	**missing**	
Plasmodium vivax	**42 (7.9)**	**missing**	
COVID-19 symptoms **N found / N available (% of available)**			
Primary COVID-19 contact	**70 / 372 (18.8)**	**2 /2 (100)**	**0.04**
Fever	**581 / 591 (98.3)**	**47 / 47 (100.0)**	**0.77**
Cough	**438 / 590 (74.1)**	**34 / 47 (72.3)**	**0.91**
Tiredness	**588 / 591 (99.5)**	**47 /47 (100.0)**	**1.0**
Chest pain	**404 / 591 (68.4)**	**30 / 47 (63.8)**	**0.63**

***None of the patients in the excluded subset had malaria diagnosis status available.**

Table 2. World Health Organization (WHO) Definition of severe *Plasmodium falciparum* malaria

Manifestations	Definitions
Impaired consciousness	**Glasgow coma score <11 in adults or Blantyre coma score <3 in children; inability to swallow**
Prostration	**Generalized weakness so that a person is unable to sit, stand, or walk without assistance**
Multiple convulsions	**More than two episodes within 24 hours**
Acidosis	**A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators of acidosis include rapid, deep, labored breathing.**
Hypoglycemia	**Blood or plasma glucose <40 mg/dL (<2.2 mmol/L) for children ≥5 years and adults; blood or plasma glucose <54 mg/dL (<3 mmol/L) for children <5 years.**
Severe anemia	**Hemoglobin concentration ≤5 g/dL or hematocrit ≤15 percent in children <12 years of age (<7 g/dL and <20 percent, respectively, in adults) with parasite count >0.25 percent parasitemia**
Renal impairment	**Plasma or serum creatinine >3 mg/dL (265 mmol/L) or blood urea >20 mmol/L**
Jaundice	**Plasma or serum bilirubin >50 mmol/L (3 mg/dL) with *Plasmodium falciparum* parasite count >2.5 percent parasitemia or *Plasmodium knowlesi* parasite count >0.5 percent parasitemia**
Pulmonary edema	**Radiographically confirmed or oxygen saturation <92 percent on room air with respiratory rate >30/minutes, often with chest indrawing and crepitation on auscultation**
Significant bleeding	**Including recurrent or prolonged bleeding (from the nose, gums, or venipuncture sites), hematemesis, or melena**
Shock	**Compensated shock is defined as capillary refill ≥3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).**
Hyperparasitemia	***Plasmodium falciparum* parasitemia >10 percent**

Severe malaria is defined as one or more of the above occurring in the absence of an identified alternative cause and in the presence of *Plasmodium falciparum* or *Plasmodium knowlesi* parasitemia.

Table 3. Population descriptive statistics stratified by region of residence.

	Non-Khartoum	Khartoum	p-value
N (% of total population)	**209 (35.4)**	**382 (64.6)**	
Demographics N (% of group)			
Age (years; mean (SD))	**59.45 (14.76)**	**57.19 (17.09)**	**0.11**
Male	**158 (75.6)**	**288 (75.4)**	**1.0**
Sudanese nationality	**202 (96.7)**	**368 (96.3)**	**1.0**
Comorbidities **N found / N available (% of available)**			
Hypertension	**59 / 181 (32.6)**	**56 / 326 (17.1)**	**<0.001**
Diabetes	**79 / 209 (37.8)**	**134 /381 (35.2)**	**0.59**
Renal disease	**13 / 209 (6.2)**	**34 / 382 (8.9)**	**0.32**
Malignancy	**11 / 209 (5.3)**	**20 / 381 (5.2)**	**1.0**
HIV	**1 / 209 (0.5)**	**6 / 382 (1.6)**	**0.43**
Cardiovascular disease	**41 / 209 (19.6)**	**57 / 382 (14.9)**	**0.26**
Neurological Disease	**15 / 169 (8.8)**	**27 / 361 (7.4)**	**0.70**
Malaria status N (% of group)			**0.001**
Malaria positive	**95 (45.5)**	**226 (59.2)**	
Plasmodium falciparum	**53 (25.4)**	**87 (22.8)**	
Plasmodium falciparum and plasmodium vivax	**59 (28.2)**	**62 (16.2)**	
Plasmodium vivax	**2 (1.0)**	**7 (1.8)**	
COVID-19 symptoms **N found / N available (% of available)**			
Primary COVID-19 contact	**12 / 82 (14.6)**	**58 / 290 (20.0)**	**0.34**
Fever	**203 / 209 (97.1)**	**378 /382 (99.0)**	**0.19**
Cough	**159/208 (76.1)**	**279/381 (73.2)**	**0.32**
Tiredness	**207 /209 (99.0)**	**381/ 381 (99.7)**	**0.60**
Chest pain	**137 /209 (65.6)**	**267/382 (69.9)**	**0.32**

Table 4. Hazard ratios for all-cause in-hospital mortality at different levels of adjustment.

Model 1: unadjusted.

Model 2: adjusted for age and gender.

Model 3: Model 2 plus hypertension, diabetes, and cardiovascular diseases.

	N (%)*	Hazard Ratios (95% CI)		
		Model 1	Model 2	Model 3**
Malaria Status	270 (46%)	1.74 (1.45-2.08)	1.75 (1.46-2.11)	1.43 (1.21 – 1.69)
Malaria species				
Plasmodium falciparum	140 (52%)	1.71 (1.39 - 2.09)	1.73 (1.36 - 2.19)	1.45 (1.14 - 1.85)
Plasmodium vivax	9 (3.0%)	2.03 (0.86 - 4.81)	1.95 (0.84 - 4.51)	2.12 (0.78 - 5.72)
Plasmodium falciparum and *Plasmodium vivax*	121 (45%)	1.76 (1.24 - 2.50)	1.77 (1.27 - 2.47)	1.39 (0.95- 2.01)

*** For malaria species, the denominator is 270 (number of malaria-positive cases), whereas for malaria status it is the whole population (591).**

** **There were 23 missing data points (8.5%) for hypertension status among subjects with malaria and 58 (18%) among non-malaria subjects. One patient in the non-malaria group (0.3%) had missing diabetes information.**

Table 5. COVID-19 symptoms

N found / N available (% of available)		
Primary COVID-19 contact identified*	**32 / 230 (13.9)**	**38 / 142 (26.8)**
Fever	**315 / 321 (98.1)**	**266 / 270 (98.5)**
Cough	**222 / 321 (69.2)**	**216 / 270 (80.0)**
Tiredness	**318 / 321 (99.1)**	**270 / 270 (100.0)**
Chest pain	**222 / 321 (69.2)**	**182 / 270 (67.4)**

Table 6. Descriptive of World Health Organization criteria for severe malaria among malaria-positive cases in the sample at presentation in the hospital

N found / N available (% of available)	Overall, N=240
Impaired consciousness	**81 / 240 (33.8)**
Prostration	**138 / 238 (58)**
Multiple convulsions	**4 / 235 (1.7)**
Acidosis	**143 / 235 (60.9)**
Hypoglycemia	**170 / 236 (72.0)**
Severe anemia	**9 / 239 (3.8)**
Renal impairment	**140 / 236 (59.3)**
Jaundice	**5 / 238 (2.1)**
Pulmonary edema	**35 / 240 (14.6)**
Significant bleeding	**12 / 237 (5.0)**
Shock	**85 / 240 (35.4)**
Hyperparasitemia	**163 / 202 (80.7)**

Table 7. Population descriptive statistics stratified by malaria severity.

	Non-severe	Severe	p-value
N (% of total population)	**23***	**240**	
Demographics N (% of group)			
Age (years; mean (SD))	**57.52 (12.8)**	**57.25 (15.3)**	**0.90**
Male sex	**18 (78.3)**	**190 (79.2)**	**1.00**
Sudanese nationality	**21 (91.3)**	**233 (97.1)**	**0.39**
Comorbidities **N found / N available (% of available)**			
Hypertension	**0 / 21 (0.0)**	**54 / 220 (24.5)**	**0.02**
Diabetes	**5 / 23 (21.7)**	**105 / 240 (43.8)**	**0.07**
Renal disease	**1 / 23 (4.3)**	**20 /240 (8.3)**	**0.79**
Malignancy	**0 /23 (0.0)**	**8 / 240 (3.3)**	**0.80**
HIV	**0 / 23 (0.0)**	**0 / 240 (0.0)**	**–**
Cardiovascular disease	**0 /23 (0.0)**	**41 / 240 (17.1)**	**0.06**
Neurological disease	**3 / 23 (13.0)**	**20 / 223 (8.9)**	**0.79**
Malaria status N (% of group)			
Malaria species			**<0.001**
Plasmodium falciparum	**5 (21.7)**	**131 (54.6)**	
Plasmodium falciparum and Plasmodium vivax	**9 (39.1)**	**109 (45.4)**	
Plasmodium vivax	**9 (39.1)**	**0 (0.0)**	
COVID-19 symptoms **N found / N available (% of available)**			
Primary COVID-19 contact	**2 / 13 (15.3)**	**34 / 126 (26.9)**	**0.60**
Fever	**22 / 23 (95.7)**	**238 / 240 (99.2)**	**0.62**
Cough	**18 / 23 (78.3)**	**191 / 239 (79.6)**	**0.94**
Tiredness	**23/ 23 (100.0)**	**240 / 240 (100.0)**	**NA**
Chest pain	**16 /23 (69.6)**	**161 / 240 (67.1)**	**0.99**

11- Appendix:

11.1- Transparency declaration

Peter Kotanko is an employee of the Renal Research Institute, a wholly-owned subsidiary of Fresenius Medical Care. Dr. Kotanko receives author royalties from UpToDate and HSTalks and holds stock in Fresenius Medical Care. Dr. Kotanko is on the Editorial Board of Blood Purification, Kidney and Blood Pressure Research, and Frontiers in Nephrology. Dr. Kotanko is the inventor of multiple patents in the field of kidney medicine.

Roberto Pcoits-Filho is employed by Arbor Research Collaborative for Health, who runs the DOPPS studies. Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. Funding is provided to Arbor Research Collaborative for Health and not to Dr. Pcoits-Filho directly. For details see https://www.dopps.org/AboutUs/Support.aspx. Dr. Pcoits-Filho receives research grants from Fresenius Medical Care, National Council for Scientific and Technological Development, honoraria (paid to an employer) from AstraZeneca, Boehringer-Lilly, Novo Nordisk, Akebia, Bayer for participation in advisory Boards and educational activities.

All other authors have declared no conflict of interest. No external funding was received.

11.2- Data Sharing:

The datasets used in the current study are available from the authors in an anonymized format upon reasonable request.

11.3- Author's contributions:

Conceptualization: Rasha Hussein, Roberto Pecoits-Filho, Peter Kotanko

Data curation: Rasha Hussein

Formal analysis: Murilo Guedes, Peter Kotanko

Investigation: Murilo Guedes, Peter Kotanko

Methodology: Rasha Hussein, Murilo Guedes, Roberto Pecoits-Filho, Peter Kotanko

Project administration: Rasha Hussein, Nada Ibraheim, Mazin M. Ali, Amal El-Tahir, Nahla Allam, Hussain Abuakar, Peter Kotanko

Software: Rasha Hussein, Murilo Guedes Nada Ibraheim, Mazin M. Ali, Amal El-Tahir, Nahla Allam, Hussain Abuakar, Peter Kotanko

Supervision: Rasha Hussein, , Nada Ibraheim , Hussain Abuakar

Validation: Rasha Hussein, Nada Ibraheim, Mazin M. Ali, Amal El-Tahir, Nahla Allam, Hussain Abuakar

Writing original draft: Rasha Hussein, Murilo Guedes, Roberto Pecoits-Filho, Peter Kotanko

Writing e review & editing: all authors.

11.4- Acknowledgements

The authors express their gratitude to UCTC health professionals and administrative staff, and the study participants. The authors appreciated the administrative help of **Maggie Han**, Renal Research Institute, New York, NY.

This manuscript is part of a PhD thesis of Rasha Hussein, at the School of Medicine, Pontifícia Universidade Catolica do Parana (PUCPR), Curitiba, Brazil. Rasha Hussein has been scientist-in-residence at the Renal Research Institute, New York, N; she is a mentee of Peter Kotanko as part of the International Society of Nephrology (ISN) Mentorship Program and the collaboration between Soba University Hospital and PUCPR has been supported by the ISN's Sister Renal Center.

11.5- Acknowledgements of Artificial Intelligence Assistance

Parts of this document were developed with the aid of artificial intelligence tools, specifically **ChatGPT**, developed by **OpenAI**, which provided guidance on structure and phrasing to enhance written clarity. AI-generated suggestions were critically evaluated and selectively integrated into the thesis, ensuring full alignment with academic standards.

12- Attachments (Parallel Production During PhD Period):

12.1. Abstract Presented at International Meeting:

1. Rasha Hussein, Peter Kotanko, et al CAUSES OF PEDIATRIC END STAGE KIDNEY DISEASE IN SUDAN, The 60th European Renal Associatin Congress in Milan June 15-18, 2023-Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023, https://doi.org/10.1093/ndt/gfad063c_4285. Published: 14 June 2023.
2. Rasha Hussein, Roberto Pecoits-Filho, et al DOES SALIVARY UREA NITROGEN DIPSTICK ALLOW PEDIATRIC ACUTE INJURY DETECTION IN SUB-SAHARAN AFRICA? World Congress of Nephrology (ISN WCN) 2020, ABU DHABI, UAE Kidney International Reports (2020) 5, S1–S392.
3. Vladimir Rigodon, Pecoits-Filho, Rasha Hussein, Peter Kotanko et al Characteristics of global dialysis data from multiple providers in the new MONitoring Dialysis Outcomes (MONDO) dataset- results from the international MONDO initiative, American Society of Nephrology, Philadelphia, 2023.
4. Vladimir Rigodon, Pecoits-Filho, Rasha Hussein, Peter Kotanko et al, Etiology of Kidney Failure Across the World in MONitoring Dialysis Outcomes (MONDO) Dataset- results from the international MONDO initiative, American Society of Nephrology, California, 2024 (Accepted).
5. Rasha Hussein, Peter Kotanko **Et al, Effectiveness of Urinary Leukocyte Test Strips for Peritonitis Screening- ISN- WCN, India 2025 (Submitted).**

12.2.Awards:

12.2.1. Sudan Intermediate Field Epidemiology Training Program (FETP):

12.2.2. ISN-Mentorship program from November 2021 to August 2023.

Introduction - ISN Mentorship Program

Pauline Vanhonsebrouck <pvanhonsebrouck@Theisn.org>
Tue 11/9/2021 8:42 AM
To:Peter Kotanko <Peter.Kotanko@RRINY.COM>;Rasha Hussein <rasha9_9@hotmail.com>

1 attachments (367 KB)
Mentorship Program Guidelines 2021.pdf;

Dear Dr. Peter Kotanko and Dr Rasha Hussein,

On behalf of Dr. Arpana Iyengar, the Chair of the Mentorship Program Advisory Group, I am pleased to confirm to you both that you have been matched and can now consider yourselves to be an ISN Mentor-Mentee pair as of today: November 9, 2021.

As a matter of introduction:
The mentor is: Dr. Peter Kotanko based in New York, USA who works at the Renal Research Institute. (peter.kotanko@rriny.com)
The mentee is: Dr. Rasha Hussein based in Khartoum, Sudan who works at Soba University Hospital. (rasha9_9@hotmail.com)

As a first tangible step in your working relationship, and to ensure that contact is established, we ask the mentee to email the mentor in order to organize a get-to-know-you session to introduce yourselves and to agree on the basic rules of cooperation (frequency of the interaction and choice of the communication platform like Zoom or Skype, etc.). Another key element is to **establish mutually agreed upon objectives** during this session, the mentee will need to clearly formulate their objectives and discuss those with the mentor. Finally, it will be important to set up a duration for the mentoring based on your objectives and agree on a timeline that works for both of you.

Could you please contact me once you will have organized this first session and send me your mutually agreed upon objectives and timeline?
Please note that you will also be asked to fill out a brief (online) **Progress Report form every 6 months**. The mentee will receive an invitation to prepare it, after which the mentor will be invited to access the report for final agreement.

I have attached the Mentorship Program Guidelines and I particularly encourage you to read our "Tips on establishing a good relationship between mentor and mentee" on page 5 and 6.

Please don't hesitate to contact mentorship@theisn.org should you ever have any questions or comments during the course of your involvement in this program.

Congratulations, we wish you a lot of success!

Best regards,

Pauline

Pauline Vanhonsebrouck
Grants & Education Project Manager
pvanhonsebrouck@theisn.org

International Society of Nephrology (ISN)

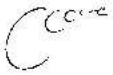
ISN Mentorship Program

The ISN Mentorship Program Advisory Group declares that:

Dr. Rasha Hussein

Mentored by Dr. **Peter Kotanko,** has successfully completed the ISN Mentorship Program from November 2021 to August 2023.

Arpana Iyengar
Lead, Mentorship Program
Advisory Group



Rolando Claure-Del Granado
Co-Lead, Mentorship Program
Advisory Group

12.2.3. ISN-Emerging Leader Program, cohort3:

Your application to the ISN Emerging Leaders Program

Sophie Dupuis <sdupuis@theisn.org>
Mon 12/11/2023 4:51 AM
To:rasha9_9@hotmail.com <rasha9_9@hotmail.com>
Cc:The ISN - ELP <elp@Theisn.org>

1 attachments (704 KB)
Dr. Hussein.pdf;

Dear Dr Hussein

You will find here attached a letter from Prof Vivekanand Jha, chair of the ISN ELP Steering Committee.
Many congratulations on a very strong and successful application!

Please read carefully the letter. We kindly ask you to confirm your acceptance in the ELP cohort by the end of the week by responding to elp@theisn.org?
If you accept, we would need to receive a picture of you as well as brief bio (as outlined in the attached letter) no later than the end of the week too.

Last but not least, thanks for keeping this news confidential for now.

Looking forward to hearing from you.

All the best,

Sophie

Sophie Dupuis
Grants & Education Director

International Society of Nephrology (ISN)
Global Operations Center
Avenue des Arts 1-2 | B-1210 Brussels | Belgium
Tel.: +32 2 808 04 20 | Fax: +32 2 808 44 54

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A close up of a sign Description automatically generated

8 December 2023

Dr. Hussein
Soba University Hospital
Sudan
rasha9_9@hotmail.com

Subject: ISN Emerging Leaders Program – Results of 2023 Application Round

Dear Dr. Hussein:

I am pleased to inform you that your application to the ISN's Emerging Leaders Program (ELP) has been accepted by the ISN ELP Steering Committee. On behalf of the ISN and the ELP Steering Committee, congratulations.

We look forward to you joining ISN's third ELP Cohort and embark on a collaborative approach to impact the kidney health agenda worldwide and play a leadership role in advancing sustainable, accessible and equitable kidney care.

This program will last for two years, starting at WCN'24 until WCN'26, and will mostly take place virtually. Some of the activities in which you will actively and regularly participate over these two years include:

- Participation in a kick-off session at WCN'24 (April 13-16, 2024 in Buenos Aires)
- Organizing some table talks and spotlight sessions at upcoming WCN'25 and WCN'26
- Affiliation as Guest with ISN Working Groups and Regional Boards
- Monthly web calls
- Webinar series on leadership
- Individual leadership profiles – Insights
- Harvard Catalyst course on Implementation Research (Fall 2024)
- Creation of an individual creative output (blog/video/other graphic/case study) followed by discussion with mentors
- Main collaborative project(s) on a kidney-related issue
- Creative group work to address today's challenges
- Capstone event at WCN'26 at which final presentations are made

Since individual commitments and schedules may have changed since you applied, please carefully consider your schedules and projects in the next two years to ensure your availability for regular and active participation in this program.

Please confirm your acceptance into the ISN ELP by responding to Sophie Dupuis (elp@theisn.org) by 15 December, 2023.

We also request you to send with your acceptance:

- a high resolution (500x500 px or more) image, preferably a full headshot
- A 50-75 word bio including a line about your expectations from this collaborative program

ISN
Advancing kidney health worldwide. Together.

Global Operations
Avenue des Arts 1-2
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United States of America
Tel: +1 347-231-1808
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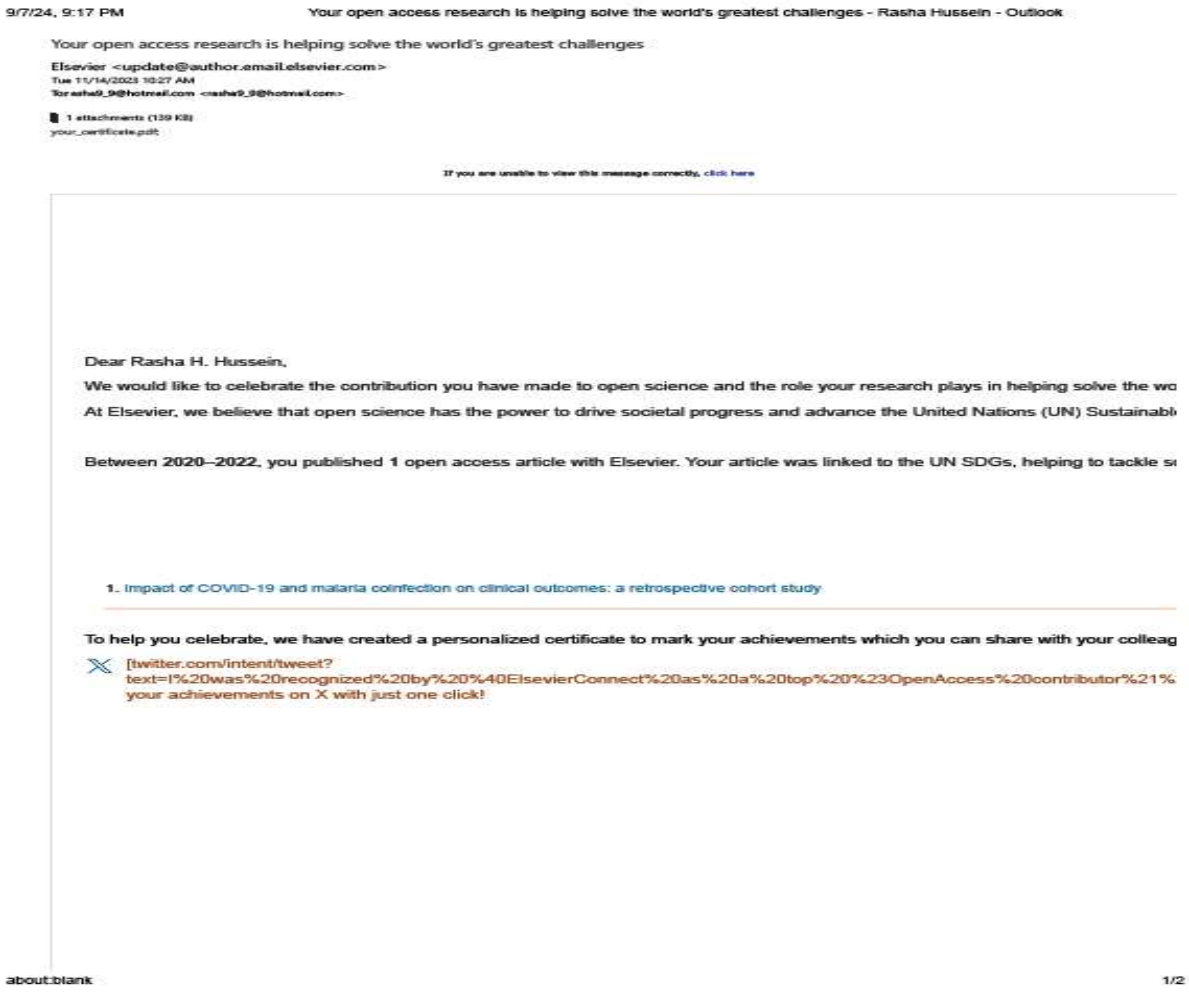
12.2.4. Certificate For publishing open science with Elsevier and the role of this research in helping solve the world's greatest challenges



9/7/24, 9:17 PM Your open access research is helping solve the world's greatest challenges - Rasha Hussein - Outlook

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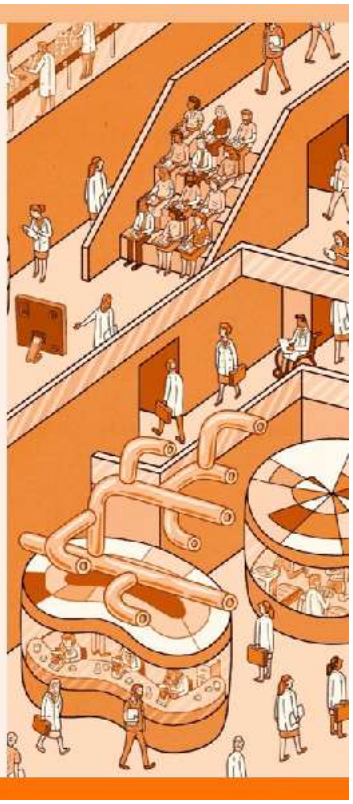

12.2.5. **Citations (40 citations from day March 31, 2022 – September 30, 2024):**

Impact of COVID-19 and malaria coinfection on clinical outcomes: a retrospective cohort study

Search within citing articles

Risk factors of severe COVID-19: a review of host, viral and environmental factors
L Zsichla, V Müller - Viruses, 2023 - mdpi.com
The clinical course and outcome of COVID-19 are highly variable, ranging from asymptomatic infections to severe disease and death. Understanding the risk factors of ...
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Protozoan co-infections and parasite influence on the efficacy of vaccines against bacterial and viral pathogens
L Akoolo, SC Rocha, N Parveen - Frontiers in Microbiology, 2022 - frontiersin.org
A wide range of protozoan pathogens either transmitted by vectors (Plasmodium, Babesia, Leishmania and Trypanosoma), by contaminated food or water (Entamoeba and Giardia), or ...
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Global Stability of a reaction–diffusion malaria/COVID-19 coinfection dynamics model
AM Elaiw, AD Al Agha - Mathematics, 2022 - mdpi.com
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new virus which infects the respiratory system and causes the coronavirus disease 2019 (COVID-19). The ...
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Co-infection of COVID-19 and parasitic diseases: A systematic review
FN Zargaran, M Rostamian, S Kooti, H Madanchi... - Parasite Epidemiology ..., 2023 - Elsevier
Co-infection of COVID-19 with other diseases increases the challenges related to its treatment management. COVID-19 co-infection with parasites is studied with low frequency ...
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Global dynamics of SARS-CoV-2/malaria model with antibody immune response.
ADA Agha, AM Elaiw - Mathematical Biosciences and Engineering ..., 2022 - europepmc.org
Coronavirus disease 2019 (COVID-19) is a new viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Malaria is a parasitic disease caused by ...
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Survival analysis of patients with COVID-19 admitted at six hospitals in Uganda in 2021: a cohort study
A Muyinda, PM Ingabire, S Nakireka... - Archives of Public ..., 2022 - Springer
Background Assessing factors associated with mortality among COVID-19 patients could guide in developing context relevant interventions to mitigate the risk. The study aimed to ...
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SARS-CoV-2 decreases malaria severity in co-infected rodent models
A Fraga, AF Mosca, D Moita, JP Simas... - Frontiers in Cellular ..., 2023 - frontiersin.org
Coronavirus disease 2019 (COVID-19) and malaria, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Plasmodium parasites, respectively, share ...
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Recent malaria does not substantially impact COVID-19 antibody response or rates of symptomatic illness in communities with high malaria and COVID-19 ...
J Woodford, I Sagara, H Diawara, MH Assadou... - Frontiers in ..., 2022 - frontiersin.org
Malaria has been hypothesized as a factor that may have reduced the severity of the COVID-19 pandemic in sub-Saharan Africa. To evaluate the effect of recent malaria on COVID-19 ...
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Increased 30-day all-cause mortality associated with Gram-negative bloodstream infections in England during the COVID-19 pandemic

T Hasan, NJ Zhu, C Pearson, P Aylin, A Holmes... - Journal of Infection, 2024 - Elsevier

Background Our aim was to assess the impact of COVID-19 pandemic on mortality in patients hospitalised with Gram-negative bloodstream infections (GNBSIs). Methods A ...

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COVID-19 and malaria co-infection: a systematic review of clinical outcomes in endemic areas

AH Mohamed, E Eltyeb, B Said, R Eltayeb, A Algaissi... - PeerJ, 2024 - peerj.com

Background COVID-19 and malaria cause significant morbidity and mortality globally. Co-infection of these diseases can worsen their impact on public health. This review aims to ...

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Incidence of Helminthic and Viral Coinfections in Malaria Patients in the Tertiary Care Hospital Setup

MA Mubaraki, M Hussain, F Fozia... - Journal of Tropical ..., 2024 - Wiley Online Library

Introduction. This study determines the incidence of common viral and helminth coinfections with malaria in the tertiary care hospital set up in southern Khyber Pakhtunkhwa, Pakistan ...

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Identification and management of co-infections in people with malaria

AJ Cunnington, A Abbara, FK Bawa, J Achan - bmj, 2024 - bmj.com

A 16 year old Ugandan girl is brought to the emergency department with a three day history of fever, headache, cough, and myalgia. She has had several episodes of malaria in the ...

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Curcumin-loaded nanomedicines as therapeutic strategy in malaria management

R Amin, C Melody Devi, D Sarkar, J Sharifi-Rad... - eFood, 2023 - Wiley Online Library

Malaria, a parasitic protozoan disease widespread in tropical climates, is transmitted by Plasmodium spp. Many people are affected by this significant public health disease, which ...

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Biogenically synthesized green silver nanoparticles exhibit antimalarial activity

S Tiwari, R Kumar, S Devi, P Sharma, NR Chaudhary... - Discover Nano, 2024 - Springer

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