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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 coinfecting 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 coinfecting 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 mono-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **Rasha Hussein, Clin Microbiol Infect 2022;28:1152.e1–1152.e6**

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## Introduction

The COVID-19 pandemic disproportionately 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].

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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-

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  $\chi^2$  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 coinfecting 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 ( $\pm 4.6$ ), 9.3 ( $\pm 4.7$ ), and 10.5 ( $\pm 4.8$ ) 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 coinfecting 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 coinfecting 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.

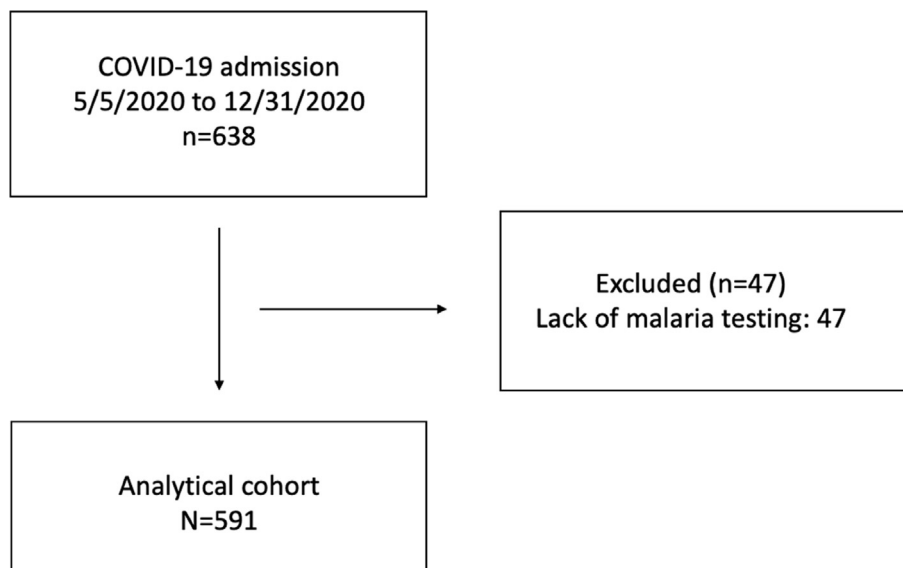
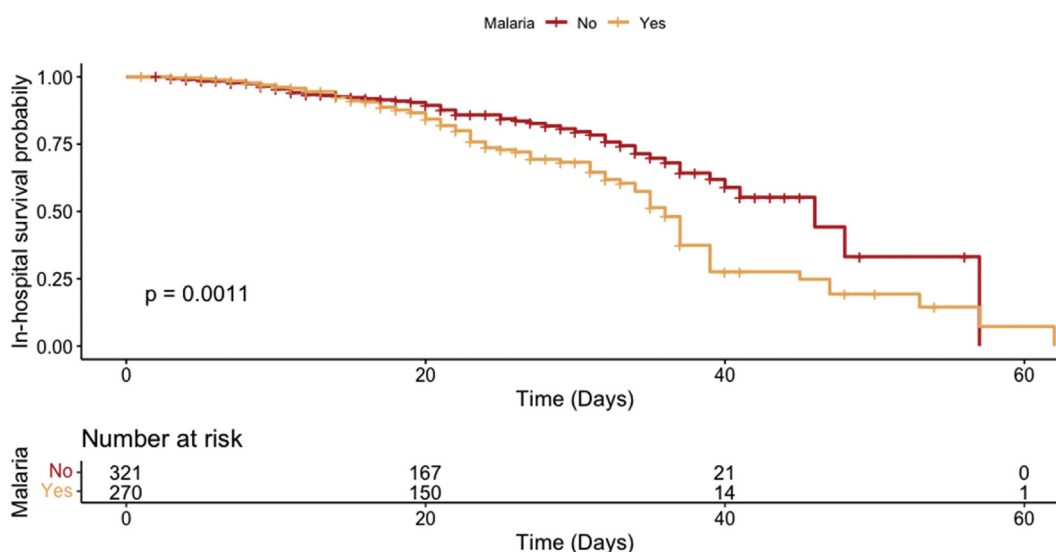


Fig. 1. Flow-chart of the selection process.

**Table 1**  
Descriptive statistics of the study population

	Without malaria	With malaria
No. (% of total population)	321 (54.3)	270 (45.7)
<b>Demographics</b> 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)
<b>Comorbidities</b> 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)
<b>Malaria species</b> No. (% of group)		
<i>Plasmodium falciparum</i>	0 (0.0)	140 (51.9)
<i>Plasmodium falciparum</i> and <i>Plasmodium vivax</i>	0 (0.0)	121 (44.8)
<i>Plasmodium vivax</i>	0 (0.0)	9 (3.3)
<b>COVID-19 symptoms</b> No. found/No. 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)



**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

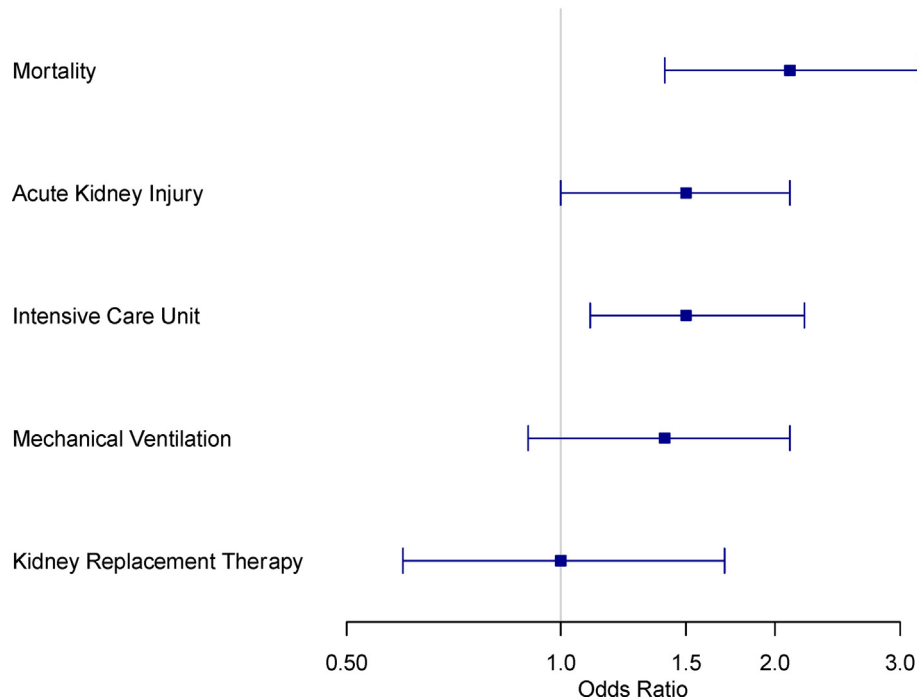
	No. (%) <sup>a</sup>	Hazard Ratios (95% CI)		
		Model 1	Model 2	Model 3 <sup>b</sup>
Malaria status	270 (46)	1.74 (1.45–2.08)	1.75 (1.46–2.11)	1.43 (1.21–1.69)
<b>Malaria species</b>				
<i>Plasmodium falciparum</i>	140 (52)	1.71 (1.39–2.09)	1.73 (1.36–2.19)	1.45 (1.14–1.85)
<i>Plasmodium vivax</i>	9 (3.0)	2.03 (0.86–4.81)	1.95 (0.84–4.51)	2.12 (0.78–5.72)
<i>Plasmodium falciparum</i> and <i>Plasmodium vivax</i>	121 (45)	1.76 (1.24–2.50)	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.

<sup>a</sup> For malaria species, the denominator is 270 (number of malaria positive cases), whereas for malaria status it is the whole population (591).

<sup>b</sup> 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.

### Association between malaria diagnosis and outcomes



**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 coinfecting healthcare workers [14]. The clinical implications of these findings are uncertain and warrant longitudinal studies of clinical outcomes among coinfecting 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 coinfecting 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 coinfecting 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 coinfecting 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, Pontifícia 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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