Title: Impact of current malaria infection and previous malaria exposure on the clinical profiles and outcome of COVID-19 in a high malaria transmission setting: a prospective cohort study

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ABSTRACT

Background

Our understanding of the potential impact of SARS-CoV-2 and malaria co-infection on host susceptibility and pathogenesis remains unclear. We determined the prevalence of malaria and describe the consequences of SARS-CoV-2 and malaria co-infection in a high burden malaria setting.

Methods

This was a prospective cohort study of hospitalized Covid-19 patients in Uganda. Malaria diagnosis was done using rapid diagnostic tests, microcopy and molecular methods. Previous *P. falciparum* exposure was assessed using serologic responses to a panel of *P. falciparum* antigens using a multiplex bead assay. Additional evaluations included complete blood count, markers of inflammation and serum biochemistries.

Findings

Of 597 PCR confirmed Covid-19 cases enrolled between 16th April and 30th October 2020, 500 (84.1%) were male and median age (1QR) was 36 (28-47) years. Overall prevalence of *P. falciparum* infection was 11.7% (70/597, 95% CI 9.4 to 14.6), with highest prevalence in the 0-20 years (21.7%, 5/23, 95% CI 8.7-44.8) and > 60 years (19.6%, 9/46, 95% CI 10.2-34.1) age groups. Confusion [5.7% (4/70) vs. 1.5%, (8/527), p=0.04] and vomiting [5.7% (5/70) vs.1.0%, 5/527), p=0.007] were more frequent among patients with *P. falciparum* infection. Patients with low previous *P.falciparum* exposure had a higher frequency of severe/critical Covid-19 cases (30.2%, 16/53, p=0.001), a higher burden of comorbidities [hypertension (30.2%, 16/53, p=0.02) and diabetes (22.6%, 12/53, p=0.003)] and more deaths (3.8%, 2/53, p=0.01). Among patients with no comorbidities, those with low previous exposure still had a higher proportion of

severe/critical Covid-19 cases (18.2%, 6/53 vs. 2.0%, 1/56, p=0.01) compared to those with high exposure.

Interpretation

Prevalence of *P. falciparum* infection among Covid-19 patients was relatively high. Though Covid-19 patients with *P. falciparum* infection had a higher frequency of confusion and vomiting, co-infection with malaria did not seem deleterious. Low previous malaria exposure was associated with severe/critical Covid-19 and adverse outcomes.

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RESEARCH IN CONTEXT

Evidence before this study

We did a general literature review to look for reports of potential interactions between SARS-CoV-2 and malaria. Several modelling studies and reports indicate that a significant number of excess cases and deaths from malaria could occur as a consequence of the SARS-CoV-2 pandemic. The assumptions in most of these models is that SARS-CoV-2 only impacts on malaria via disruption to control measures with limited direct interactions between the two diseases.

Added value of this study

This comprehensive prospective study is the first to characterise potential interactions between SARS-COV-2 and malaria and describe important clinical correlates of coinfection n a high burden malaria setting.

Implications of all the available evidence

A better understanding of the nature of interactions between SARS-COV-2 and malaria is of significant public health interest especially in sub-Saharan Africa given the potential for epidemiological overlap. This knowledge could inform response efforts and promote integrated approaches to investigations and management.

BACKGROUND

The SARS-CoV-2 virus has caused considerable morbidity and mortality globally, with over 118 million cases and 2.6 million deaths reported by 10th March 2021(1). Since the first cases were reported in Africa on 14th February 2020, SARS-CoV-2 has spread to all countries in the continent and has caused unprecedented socioeconomic and healthcare systems disruptions. Though sub-Saharan Africa currently has a relatively low global portion of the coronavirus disease 2019 (Covid-19) cases and deaths compared to other continents (2), it disproportionately has a higher burden of other infectious diseases (3-5). The potential impact of Covid-19 on the control of these diseases and the potential implications of any clinical interactions between Covid-19 and these infections therefore remains a major public health concern in Africa especially when geographic overlap results in high levels of co-infection. However, despite the global spread of SARS-CoV-2, our understanding of the epidemiology and clinical course of Covid-19 in countries with substantial burdens of other infectious diseases is limited. The magnitude of clinical overlap between these diseases and Covid-19 and the potential consequences of co-infection also remains largely unknown.

Whereas predictive models suggest possibly lower mortality from Covid-19 in low- and middle-income countries (LMICs) than that in high-income countries (6), several modelling studies and reports indicate that a significant number of excess cases and deaths from HIV/AIDs, tuberculosis, and malaria could occur as a consequence of the Covid-19 pandemic (7-11). However, the assumptions in some of these models that one disease doesn't directly influence the transmission or severity of the other and that Covid-19 only impacts on these diseases via disruption to control measures and effects on the health system, may be flawed. Of particular interest among these infections is malaria which causes significant morbidity and mortality with

an estimated 229 million cases and 409,000 deaths reported globally in 2019 alone (> 90% in sub-Saharan Africa) (3). If co-infections like malaria increase complications with SARS-CoV-2 infection, then the burden of Covid-19 in LMICs could be substantially worse than predicted. It is also unclear whether immunomodulation caused by malaria (12, 13) is beneficial or harmful in the context of co-infection with SARS-CoV-2. Malaria-induced immunomodulation has been shown to be protective against severe manifestations of some respiratory viruses (14) by suppressing production of cytokines and decreasing recruitment of cellular inflammatory components to the lungs, leading to milder clinical symptoms and inflammation (15). Prior exposure to or preexisting infection with malaria could therefore plausibly lead to changes in susceptibility and/or severity of Covid-19 (16). However, despite these observations, the impact of malaria and SARS-CoV-2 co-infection on host susceptibility and pathogenesis remains unclear. It's against this background that this study was conducted to better characterize Covid-19 cases in a high malaria burden setting and to determine the prevalence of and describe the clinical consequences of SARS-CoV-2 and malaria co-infection.

METHODS

Study design and participants

This was a prospective cohort study conducted from 15th April to 30th October 2020 at Covid-19 treatment centers in eight tertiary hospitals in Uganda. These included Mulago, Entebbe and Bombo in central, Gulu and Lira in the north, Jinja in the east, Masaka in the south and Arua in the north-western regions of Uganda respectively (Figure S1). Using consecutive sampling, hospitalised Covid-19 patients of all ages, with a PCR confirmed diagnosis were enrolled. The study was approved by the Mulago National Referral Hospital Research and Ethics committee and the Uganda National Council for Science and Technology. Written informed

consent was obtained from patients or their next of kin and assent from patients aged 8 – 17 years.

Clinical procedures

Demographic and clinical information collected included age, gender, presenting complaints, underlying medical conditions, duration of illness, clinical examination findings, diagnosis and medications prescribed. Patients were followed up until discharge/death and clinical outcomes and duration of hospitalization were noted. Covid-19 management was done according to national guidelines and malaria treatment was based on rapid diagnostic test (RDT) results.

Laboratory procedures

Malaria diagnosis was done using RDTs (Paracheck Pf, from Orchid Biomedical System, India), microcopy and molecular methods. For microscopy, thick blood smears were stained with 2% Giemsa and examined by two independent microscopists. Discrepancies were settled by a third reader. Parasite density was estimated by counting the number of parasites per 200 WBC, and assuming 8,000 WBC/μL. Blood smears were considered negative if no parasites were found after reading 100 high power fields. Molecular detection of *P. falciparum* was done using established methodologies (17). Extracted DNA was analysed with varATS qPCR using 5μL of extracted DNA per assay. All qPCR outputs were analysed using the BioRad CFX Manager software. The sensitivity of the assay was approximately 0.02 parasites/μL of blood. Previous individual *P. falciparum* exposure was assessed using serologic responses to a panel of *P. falciparum* antigens using a multiplex bead assay as previously described (18). These included responses associated with cumulative malaria exposure, namely apical membrane antigen-1 (AMA-1), merozoite surface protein1.19 (MSP1.19) and glutamate-rich protein (GLURP.R2) (18, 19), and responses associated with malaria infection in the past 6 months, namely

reticulocyte-binding protein homologue (Rh2.2030), gametocyte exported protein (GEXP18) and Early transcribed membrane protein (Etramp5.Ag1) (20). Additional evaluations at presentation included complete blood count, markers of inflammation like C-Reactive protein (CRP), interleukin (IL)-2, IL-6, IL-7, IL-8, IL-10, transforming growth factor beta (TGF-β1) and tumor necrosis factor alpha (TNF-α); liver and renal function, and HIV tests. Serum cytokines were tested using BD FACSCalibur flow cytometer (BD FACSCalibur, BD Bioscience, CA) and human Th1/Th2 cytokines kit (Bio-Techne Ltd, Abingdon, UK) following manufacturers' instructions. Laboratory personnel were blinded to patients' clinical status to avoid potential bias.

Statistical analysis

A sample size of 600 participants was estimated assuming a total available patient population of 800 during the course of the study, a margin of error of 0.02 and 95% level of confidence. Categorisation of serological responses was conducted as in Achan et al. with highest and lowest deciles used to differentiate high and low exposure (19). Descriptive statistics were computed for continuous and categorical variables. Medians with interquartile ranges were calculated for skewed data distributions and means with standard deviations for normally distributed data. Proportions were computed for categorical variables. Statistical comparisons between subgroups of continuous variables were evaluated by *t*-test, analysis of variance, Mann-Whitney U tests, and Kruskal-Wallis tests where appropriate. For immunological analyses, differences were assessed by comparing mean values between groups using either a two-tailed Student's t-test or non-parametric equivalents. A forward fitting logistics regression model was used to determine predictors of unfavorable outcomes. Kaplan-Meier survival analysis was used to estimate recovery rates and comparisons done using Log-rank tests. Analyses were done using STATA

V.15.0 and $p<0.05$ based on a two-sided hypothesis was considered significant. Where data were missing, the numbers involved are stated and no attempt was made to impute missing values.

RESULTS

Sociodemographic and clinical characteristics of study patients

Of 600 Covid-19 patients enrolled and followed up, we analyzed 597 (99.5%) with complete information (Figure 1). Table S1 summarizes patient characteristics at admission. The majority (84.1%, 500/597) were male, median age (1QR) was 36 (28-47) years, with 7.7% (46/597) aged > 60 years and 3.9% (23/597) aged ≤ 20 years. Long distance truck drivers constituted 37.6% (169/450) and 4.9% (22/450) were health care workers. Comorbidities were reported by 39.0% (233/597) of the patients with hypertension (16.4%, 98/597), diabetes (8.2%, 49/597), and HIV (6.2%, 35/565) being the most prevalent. The commonest symptoms at presentation included cough (33.2%, 198/597), runny nose (21.6%, 129/597), fever (20.4%, 122/597), headache (18.8%, 112/597), shortness of breath (16.6%, 99/597) and chest pain (14.2%, 85/597). The median (IQR) temperature was 36.5^0 C (36.3-36.7) and only 4.8% (26/545) of the patients had a documented temperature ≥ 37.5^0 C. The median (IQR) respiratory rate was 18 breathes/min (16-21) but this was assessed in only 33.8% (202/597) of the patients. Overall, 42.8 % (250/584) were asymptomatic; 38.7% (226/584) had mild, 7.5% (44/584) moderate, 8.2% (48/584) severe and 2.7% (16/584) had critical Covid-19, with 50 patients (8.4%) admitted for intensive care. The mean (SD) duration of hospitalization was 17.4 (4.6) days and 20.8% (115/553) were hospitalized for > 21 days. The majority of patients (78.9%, 471/597) were discharged in good general condition and only 1.5% (9/597) died.

P. falciparum infection and Covid-19 clinical presentation and outcome

The overall prevalence of *P. falciparum* infection (defined as positive by either RDT, microscopy or PCR) was 11.7% (70/597, 95% CI 9.4 to 14.6) (Table 1). The highest prevalence was observed in the 0-20 years (21.7%, 95% CI 8.7-44.8) and > 60 years (19.6%, 95% CI 10.2-34.1) age groups. The median (IQR) parasite density was 104/µL (32-1010). Patients with *P. falciparum* infection had a higher frequency of confusion (5.7% vs 1.5%, p=0.04) and vomiting (5.7% vs.1.0%, p=0.007) compared to those without malaria (Table 3). There were no differences in gender, occupation, fever, headache and duration of hospitalization between Covid-19 patients with and without *P. falciparum* infection. Mean (SD) platelet count [216400 (10500) vs. 240100 (3900), p = 0.04] and serum albumin levels [38.8 (1.4) vs. 42.1 (0.4), p=0.008] were significantly lower in Covid-19 patients with *P. falciparum* infection (Table S3). Overall, *P. falciparum* positive patients had a lower prevalence of liver function abnormalities and lower median liver enzyme levels (Table S3) with statistically significant elevations in gamma-glutamyl transferase (GGT) [6.9% (4/58) vs. 17.8% (81/456), p=0.04] and total protein [70.7% (41/58) vs. 83.4% (367/440), p=0.02]. There was a non-significant trend towards lower mean (SD) hemoglobin [14.6 (0.3) vs 15.1 (0.1), p=0.06] and higher HIV prevalence [7 (10.9% vs. 28 (5.9%), p=0.12] among Covid-19 patients with *P. falciparum* infection (Table S3). Kaplan-Meier survival analysis showed a lower probability of unfavorable outcome among patients with *P. falciparum* infection but this was not statistically significant (log rank p = 0.55) (Figure S2A).

Previous malaria exposure and Covid-19 clinical presentation and outcome

Patients with low previous *P. falciparum* exposure were older with mean age (SD) of 45.8 years (12.7) compared to 37.6 years (13.1) and 37.5 years (12.7) in the medium and high exposure

groups respectively, $p < 0.001$ (Table 2). The low exposure group also had a higher frequency of fever (32.1%, $p = 0.01$), cough (50.9%, p=0.001), shortness of breath (43.4%, p= 0.001) and chest pain (32.1%, p=0.001). Patients with low previous exposure were more likely to present with severe/critical Covid-19 (30.2%, p=0.001), have a higher burden of comorbidities including hypertension (30.2%, p=0.024) and diabetes (22.6%, p=0.003), higher proportion of intensive care admissions (18.9%, p=0.01) and more deaths (3.8%, p=0.01) (Table 2). Median antibody responses to individual *P. falciparum* antigens were significantly lower in patients with severe/critical Covid-19 but the differences were modest for Etramp5.Ag1 (Figure. 2). Patients with low previous exposure had a higher probability of having an unfavorable outcome, though this was not statistically significant (log rank $p = 0.66$) (Figure S2B). No patients in the high previous exposure group died.

To better understand the relation between previous *P.falciparum* exposure and Covid-19 clinical presentation and outcomes, we further categorised the patients into two groups, those with comorbidities and those without comorbidities. Among patients with comorbidities, the low exposure group had a higher frequency of shortness of breath (70%, 14/20 vs. 14.3%, 1/7, p=0.04), severe/critical cases (50%, 10/20 vs. 28.6%, 2/7, p=0.52), and unfavorable outcomes (40%, 8/20 vs 28.6%, 2/7, p= 0.53) when compared to the high exposure group though the latter two differences were not statistically significant. Among those with no comorbidities, the low exposure group had a higher frequency of fever (33.3%, 11/53 vs. 8.3%, 4/56, p=0.02), shortness of breath (27.3%, 9/53 vs. 2.1%, 1/56, p=0.002), chest pain (24.3%, 8/53 vs. 4.2%, 2/56, p=0.01) and severe/critical cases (18.2%, 6/53 vs. 2.0%, 1/56, p=0.01) when compared to the high exposure group.

Cytokine profiles, Covid-19 disease severity and malaria status

There were no significant differences in cytokine levels among *P. falciparum* positive and negative patients except for TNF-α which was significantly higher in positive patients (5.4 pg/mL, coef. 0.6, p=0.001) (Table S2). Patients with medium and high previous malaria exposure had significantly lower levels of IL-7 (7.9 pg/mL, coef. -2.2, p=0.004, and 5.2 pg/mL, coef. -5.6, p=0.001, respectively) and TGF-β1 (166,932 pg/mL, coef. -34813.9, p=0.026 and 116,307 pg/mL, coef. -85439.2, p=0.001; respectively) when compared to the low exposure group (Table S2). Cytokine levels also varied with severity of Covid-19 with higher IL-6 levels in patients with moderate (10.8 pg/mL, coef. 9.3, p=0.001) and severe/critical Covid-19 (13.0 pg/mL, coef.11.5, p=0.001) and higher IL-7 levels among patients with moderate (12.7 pg/mL, coef. 6.5, p=0.001) and severe/critical Covid-19 (13.9 pg/mL, coef.7.7, p=0.001). Both TNF-α and TGF-β1 levels were higher in patients with severe/critical Covid-19 (5.4 pg/mL, coef. 0.6, p=0.004 and 192,485 pg/mL, coef. 30,028, p=0.05; respectively) compared to the other clinical categories. IL-8 levels were lowest among patients with mild Covid-19 (28.4 pg/mL, coef. -24.7, p=0.009) and did not significantly vary with *P. falciparum* infection, previous malaria exposure or clinical outcomes. No significant elevation in IL-2 was observed in this patient population. Unfavorable outcomes were associated with high levels of IL-6 ((20.1 pg/mL, coef. 17.3, p=0.001), TNF-α (5.8 pg/mL, coef. 0.9, p=0.029) and IL-10 (160 pg/mL, coef. 149.1, p=0.001) (Table 4).

Predictors of unfavorable outcomes among Covid-19 patients

Overall, 12.2 % (73/597) patients had an unfavorable outcome, defined as death, discharge with sequelae or requiring intensive care. Age > 60 years and HIV infection were associated with significantly higher odds of unfavorable outcomes [adjusted OR 5.1 (2.1-12.3), p=0.001] and

[adjusted OR 2.8 (1.0-7.9), p=0.05] respectively. There was a non-significant trend towards higher odds of unfavorable outcomes among patients with diabetes [adjusted OR 2.2 (0.9-5.2), P=0.08]. High ALT [adjusted OR 2.0 (1.0-4.0), p=0.04], low serum albumin [adjusted OR 2.5(1.2-5.1), p=0.01], high urea levels [adjusted OR 4.2(2.0-8.5), p=0.001], high CRP levels [adjusted OR 2.8(1.5-5.0), p=0.001] and high IL-6 levels [adjusted OR 4.4(2.6-7.6), p=0.001] were associated with higher odds of unfavorable outcomes. Patients with high neutrophil counts had a lower likelihood of unfavorable outcomes [adjusted OR 0.3 (0.1-0.9), p=0.03].

DISCUSSION

This study reports the prevalence of and describes the clinical consequences of SARS-CoV-2 and malaria co-infection, and assesses the impact of previous malaria exposure on Covid-19 clinical presentation and outcomes. To our knowledge, this study is the first to characterise potential interactions between SARS-COV-2 and malaria. In this hospitalized cohort of Covid-19 patients, the overall prevalence of malaria was 11.7%, higher than the national average prevalence of 9% (21), but similar to some regional estimates in the country (21). In malaria endemic settings like Uganda, malaria disease burden is largely in infants and young children, so the significant burden of *P.falciparum* infection among Covid-19 patients > 60 years of age in this study is intriguing and requires further investigation.

Given the significant symptom overlap between Covid-19 and malaria, the higher frequency of confusion and vomiting and the distinct laboratory profiles of Covid-19 patients with *P. falciparum* infection are important clinical correlates that should trigger investigations for malaria and ensure integrated management. The higher prevalence of HIV among Covid-19 patients with malaria though non-significant, requires further evaluation to better understand the clinical implications of all three co-infections at the individual patient level. The overall trend

towards a lower probability of unfavourable outcomes in Covid-19 patients with *P. falciparum* co-infection is encouraging and could suggest that immunomodulation caused by malaria (12-14) may not be deleterious. The association of low previous *P. falciparum* exposure with severe/critical Covid-19 and a trend towards higher probability of unfavourable outcomes is novel. However, patients in the low exposure group were also older and had a higher burden of comorbidities including hypertension and diabetes. Since both age and co-morbidities are associated with severe/critical Covid-19 and more adverse outcomes (22-24); the correlation between previous malaria exposure and Covid-19 clinical presentation and outcomes will require further study. However, findings among Covid-19 patients without comorbidities indicate that the association of low previous exposure with more severe manifestations of Covid-19 remains even in the absence of comorbidities. This is an important observation that could imply that malaria exposure may have a role in the pathogenesis of Covid-19 in these settings.

Whereas cytokine profiles in Covid-19 patients in low malaria burden settings have been well characterised, there's limited data from high burden settings. In this study, TNF-α levels were higher among patients with *P. falciparum* infection, IL-7 and TGF-β1 levels were higher among patients with low malaria exposure and IL-6, IL-10, TNF-α and TGF-β1 levels were higher among patients with more severe manifestations and adverse outcomes. Our findings are similar to accumulating evidence that suggests that severity of Covid-19 is associated with an increase in cytokines and chemokines including IL-2, IL-7, IL-10, TNF-α, CRP and IL-6, with the latter highly correlated with mortality (25, 26). With the exception of TNF-α, *P. falciparum* infection did not significantly impact on cytokine levels in this population. This could suggest a blunting of cytokine and chemokine responses to malaria that has been shown to occur in older children and adults residing in endemic areas, which may be due to repeated malaria exposure (27). These

findings are further supported by the relatively normal cytokine profiles among patients with high previous exposure in this study. Therefore, the unique balance between pro-inflammatory and anti-inflammatory cytokines could explain the clinical observations among co-infected patients.

The overall mortality in this population of 1.5% is significantly lower than that in Europe and China (28-30); but similar to that reported in other malaria endemic settings (30). Predictors of unfavourable outcome like age and high IL-6 levels are consistent with those previously described (25, 26). It is however concerning that HIV infection was associated with unfavourable outcomes. Given the high burden of HIV in sub-Saharan Africa, this has significant public health implications that need to be addressed.

This study had some limitations including limited sample size of *P. falciparum* positive patients, and lack of information on SARS-CoV-2 viral load and radiology. Despite this, the strengths of this study include the prospective design, broad eligibility criteria, limited loss to follow up and robust malaria diagnostic and immunology assays.

In conclusion, the prevalence of P falciparum infection among hospitalized Covid-19 patients in this high burden malaria setting was relatively high (11.7%). Though low previous malaria exposure was associated with more severe Covid-19 and higher probability of adverse outcomes, current *P. falciparum* infection was not deleterious. Additional studies are required to further explore the associations observed in this study.

Contributors

JA and JT conceived and designed the study. JA, AS, IS, HA and FN were involved in study implementation and data collection. JA, HW and IS did the statistical analysis. JA drafted the first version of the manuscript. JA, JT, AS, HW and IS had access to and verified the study data. All authors contributed to data review and interpretation, and finalized and approved the manuscript.

Declaration of interest

HA and FN are members of the Mulago Hospital Research and Ethics but did not participate in decisions pertaining this study. All other authors declare no competing interests.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data Sharing

All data requests should be submitted to the corresponding author (JA) for consideration. Requests will be assessed for scientific rigor before being granted. Data will be anonymized and securely transferred. Patient-level data will be made available within 6 months of publication. Related documents will be available on request. A data sharing agreement may be required.

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Figure Legends

Figure 1. Study flow chart

Figure 2. Dot plots comparing individual *P. falciparum* antibody responses and severity of Covid-19

Figure 1. Study flow chart

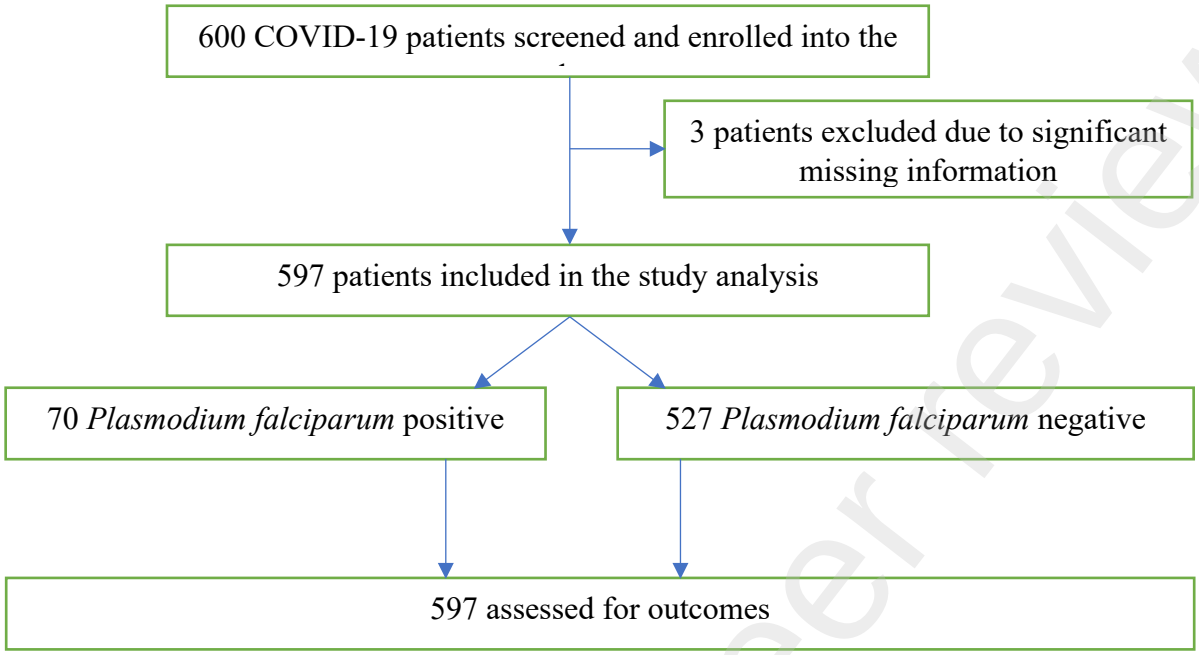
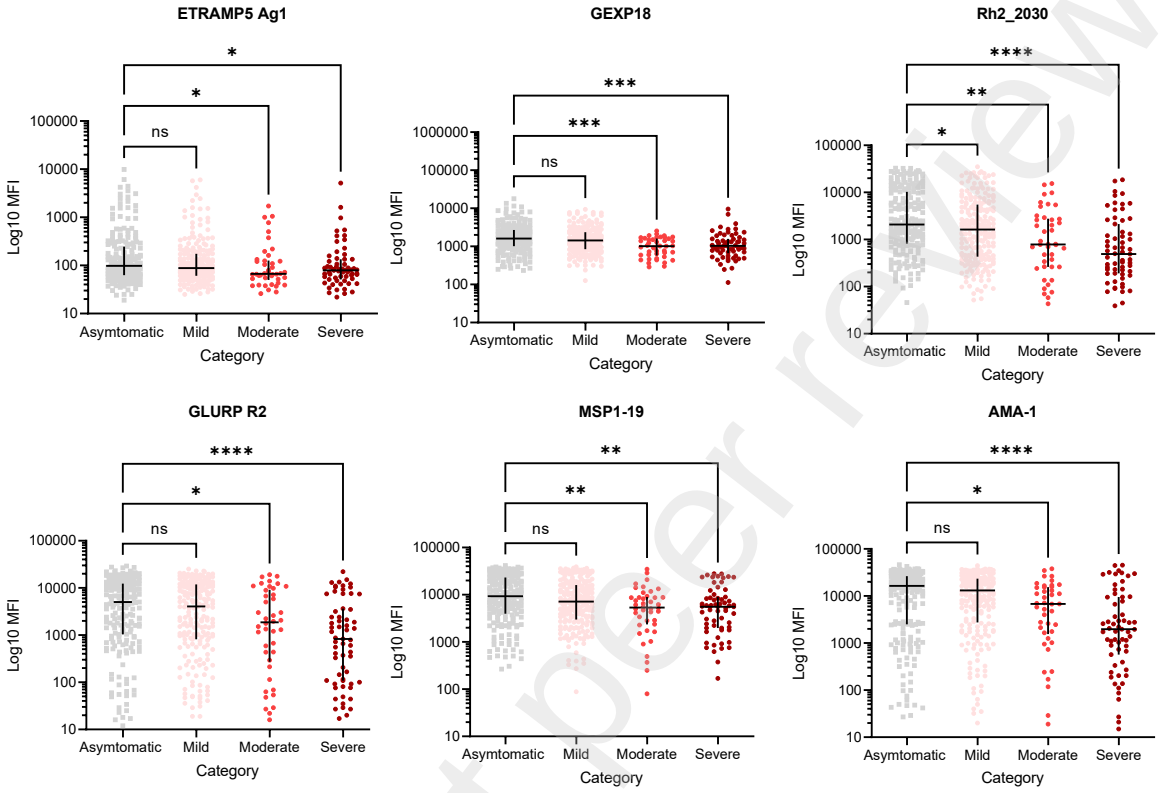


Table 1. *P. falciparum* infection and previous malaria exposure among Covid-19 patients

Malaria variable	n/N	Prevalence (95% CI)
P. falciparum infection*	70/597	11.7 (9.4 – 14.6)
P. falciparum infection by age*		
0-20	5/23	21.7 (8.7 – 44.8)
21-40	33/355	9.23 (6.7 – 12.8)
41-60	20/163	12.3 (8.0 – 18.3)
>60	9/46	19.6 (10.2 – 34.1)
Previous malaria exposure		
Low	53/527	10.1 (7.8 – 12.9)
Medium	418/527	79.3 (75.6 – 82.6)
High	56/527	10.6 (8.3 – 13.6)

*Defined as positive by either RDT, microscopy or molecular methods (PCR)

Figure 2. Dot plots comparing individual *P. falciparum* antibody responses and severity of Covid-19



A total of 513 patients (195 asymptomatic, 213 mild, 42 moderate and 63 severe/critical) were included in this analysis. Plots represent median (interquartile range) mean fluorescent intensities with multiple comparisons made against the asymptomatic group. P values are represented by stars; * = 0.05-0.005, ** = 0.005-0.001, ***< 0.001

Table 2. Association between clinical parameters among Covid-19 patients with *P. falciparum* infection and previous malaria exposure

Clinical parameter	Overall N = 597	Covid-19 patients by malaria category						
		Current malaria infection			Previous malaria exposure			
		Malaria N = 70	No malaria N = 527	Chi-square p-value	Low N = 53	Moderate N = 418	High N = 56	Chi-square p-value
Presence of signs and symptoms								
Fever	121 (20.3)	15 (21.4)	106 (20.1)	0.81	17 (32.1)	92 (22.0)	6 (10.7)	**0.01**
Cough	198 (33.2)	19 (27.1)	179 (34.0)	0.39	27 (50.9)	150 (35.9)	13 (23.2)	**0.001**
Flu	129 (21.6)	11 (15.7)	118 (22.4)	0.44	9 (17.0)	103 (24.6)	10 (17.9)	0.07
Shortness of breath	98 (16.4)	13 (18.6)	85 (16.1)	0.61	23 (43.4)	71 (17.0)	3 (5.4)	**0.001**
Muscle pains	22 (3.7)	3 (4.3)	19 (3.6)	0.94	0 (0)	20 (4.8)	1 (1.8)	0.16
Confusion	12 (2.0)	4 (5.7)	8 (1.5)	**0.04**	1 (1.9)	9 (2.2)	0 (0)	0.77
Headache	112 (18.8)	16 (22.9)	96 (18.2)	0.53	13 (24.5)	81 (19.4)	11 (19.6)	0.36
Sore throat	49 (8.2)	2 (2.9)	47 (8.9)	0.21	5 (9.4)	38 (9.1)	4 (7.1)	0.53
Chest pain	84 (14.1)	8 (11.4)	76 (14.4)	0.78	17 (32.1)	61 (14.6)	4 (7.1)	**0.001**
Diarrhoea	20 (3.4)	4 (5.7)	16 (3.0)	0.42	3 (5.7)	16 (3.8)	1 (1.8)	0.45
Vomiting	9 (1.5)	4 (5.7)	5 (1.0)	**0.007**	0 (0)	7 (1.7)	2 (3.6)	0.50
Fatigue	17 (2.9)	1 (1.4)	16 (3.0)	0.70	3 (5.7)	13 (3.1)	0 (0)	0.48
Red	4 (0.7)	0 (0)	4 (0.8)	0.75	1 (1.9)	3 (0.7)	0 (0)	0.42
Covid-19 Severity								
Asymptomatic	250 (42.9)	36 (51.4)	214 (40.6)		12 (22.6)	151 (36.1)	32 (57.1)	
Mild	225 (38.6)	17 (24.3)	208 (39.5)		16 (30.2)	179 (42.8)	17 (30.4)	
Moderate	44 (7.6)	6 (8.6)	38 (7.2)		7 (13.2)	35 (8.4)	0 (0)	
Severe/critical	64 (11.0)	10 (14.3)	54 (10.3)	0.14	16 (30.2)	45 (10.8)	3 (5.4)	**0.001**
Co-morbidities								
Tuberculosis	3 (0.5)	0 (0)	3 (0.6)	0.63	0 (0)	3 (0.7)	0 (0)	0.80
Diabetes	49 (8.2)	7 (10.0)	42 (8.0)	0.70	12 (22.6)	28 (6.7)	2 (3.6)	**0.003**
COPD	1 (0.2)	1 (1.4)	0 (0)	**0.02**	0 (0)	1 (0.2)	0 (0)	0.90
Asthma	8 (1.3)	0 (0)	8 (1.5)	0.30	4 (7.6)	4 (1.0)	0 (0)	**0.003**
Obesity	16 (2.7)	3 (4.3)	13 (2.5)	0.46	5 (9.4)	10 (2.4)	1 (1.8)	**0.04**
Heart disease	23 (3.9)	2 (2.9)	21 (4.0)	0.48	7 (13.2)	14 (3.4)	0 (0)	**0.01**
HIV	35 (5.9)	5 (7.1)	30 (5.7)	0.80	1 (1.9)	21 (5.0)	4 (7.1)	**0.02**
Hypertension	98 (16.4)	9 (12.9)	89 (16.9)	0.39	16 (30.2)	65 (15.6)	8 (14.3)	**0.02**
Clinical outcomes								
Discharged in good condition	471 (78.9)	53 (75.7)	418 (79.3)		33 (62.3)	327 (78.2)	46 (82.1)	
Discharged with sequelae	10 (1.7)	0 (0)	10 (1.9)		0 (0)	9 (2.15)	0 (0)	
Admitted for Intensive care	50 (8.4)	9 (12.9)	41 (7.8)		10 (18.9)	36 (8.6)	4 (7.1)	
Died	9 (1.5)	2 (2.9)	7(1.33)	0.36	2 (3.8)	7(1.7)	0 (0)	**0.01**

Table 3. Clinical factors associated with unfavorable outcome among Covid-19 patients

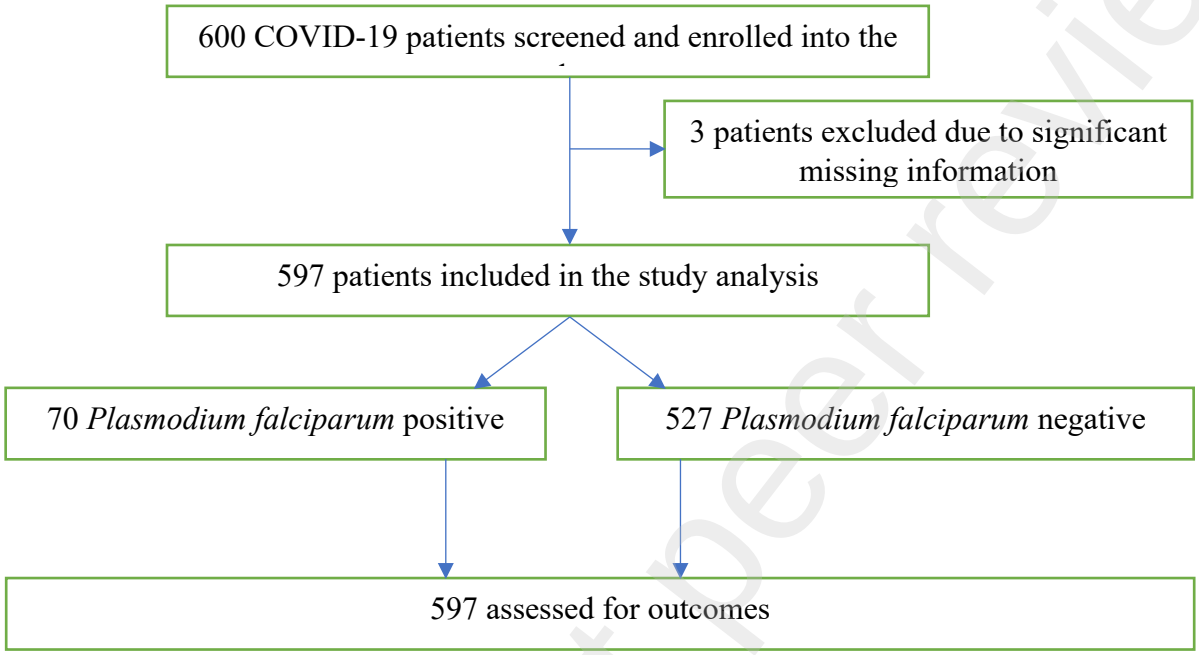
Patient attribute	Covid-19 patient outcomes				
	Unfavorable outcome* N = 73	Discharged in good condition N = 524	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Age categories					
0-40	34 (47.9)	344 (66.7)	1	1	
41-60	18 (25.4)	145 (28.1)	1.3 (0.7-2.3)	1.1 (0.6-2.2)	0.75
>60	19 (26.8)	27 (5.2)	7.1 (3.6-14.1)	5.1 (2.1-12.3)	**0.001**
Gender					
Male	59 (80.82)	443 (84.5)	1	1	
Female	14 (19.18)	81 (15.5)	1.3 (0.7-2.4)	0.9 (0.4-1.9)	0.80
Current Malaria infection					
Negative	65 (89.0)	462 (88.2)	1	1	
Positive	8 (11.0)	62 (11.8)	0.9 (0.4-2.0)	0.9 (0.3-2.0)	0.65
Previous malaria exposure					
Moderate	53 (76.8)	365 (79.7)	1	1	
Low	10 (14.5)	43 (9.4)	1.6 (0.8-3.4)	1.2 (0.5-2.9)	0.65
High	6 (8.7)	50 (10.9)	0.8 (0.3-2.0)	1.0 (0.4-2.6)	0.99
Diabetes					
No	57 (78.1)	488 (93.7)	1	1	
Yes	16 (21.9)	33 (6.3)	4.2 (2.2-8.0)	2.2 (0.9-5.2)	0.08
COPD/Asthma					
No	69 (97.2)	513 (98.7)	1	1	
Yes	2 (2.8)	7 (1.4)	2.1 (0.4-10.4)	1.8 (0.5-74.8)	0.66
HIV					
No	63 (91.3)	471 (94.2)	1	1	
Yes	6 (8.7)	29 (5.8)	1.5 (0.6-3.9)	2.8 (1.0-7.9)	**0.05**
High blood pressure					
≥130/90	61 (83.6)	438 (83.6)	1	1	
≥140/90	12 (16.4)	86 (16.4)	1.0 (0.5-1.9)	1.0 (0.5-2.7)	0.97
Heart disease					
No	7 (9.9)	16 (3.1)	1	1	
Yes	64 (90.1)	501 (96.9)	0.3 (0.1-0.7)	0.6 (0.2-1.7)	0.31

*Defined as death, discharge with sequelae or requiring intensive care

Title: Impact of current malaria infection and previous malaria exposure on Covid-19

Figures

Figure 1. Study flow chart



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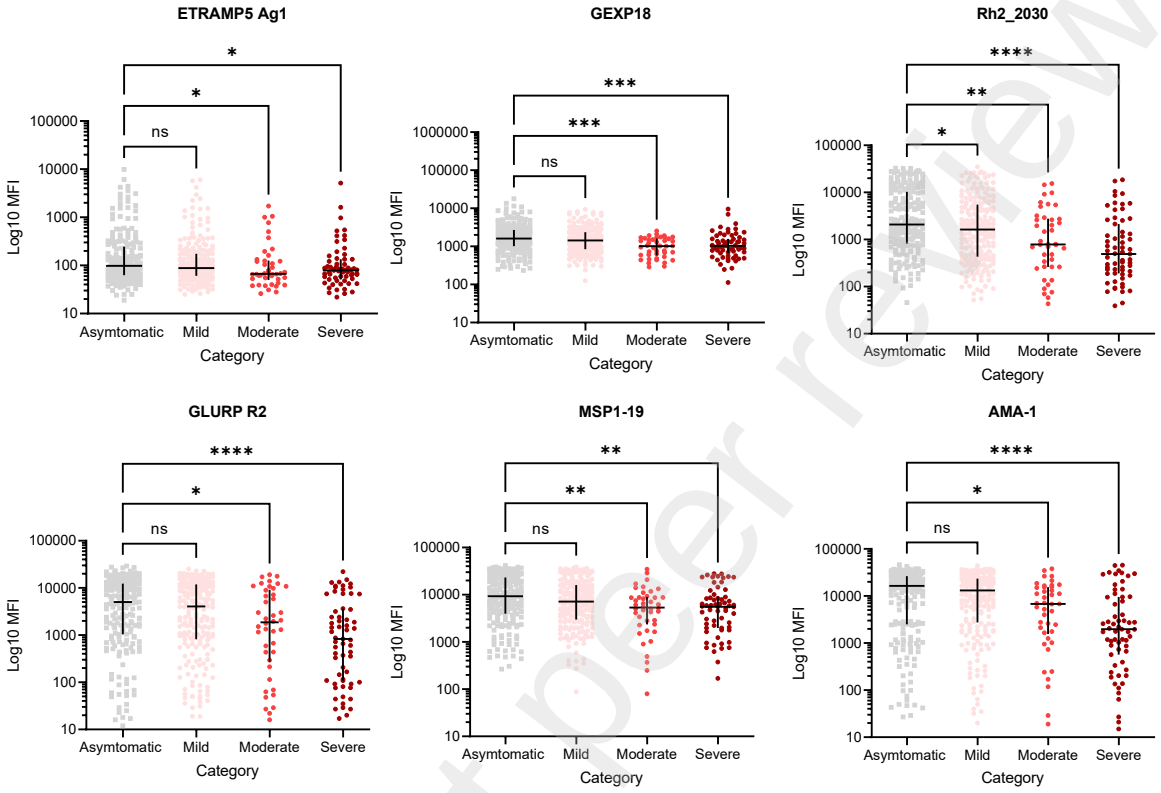

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