# Impact of current malaria infection and previous malaria exposure on clinical profiles and outcomes of COVID-19 in a high malaria transmission setting: A prospective cohort study

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Covid-19 and malaria global distribution
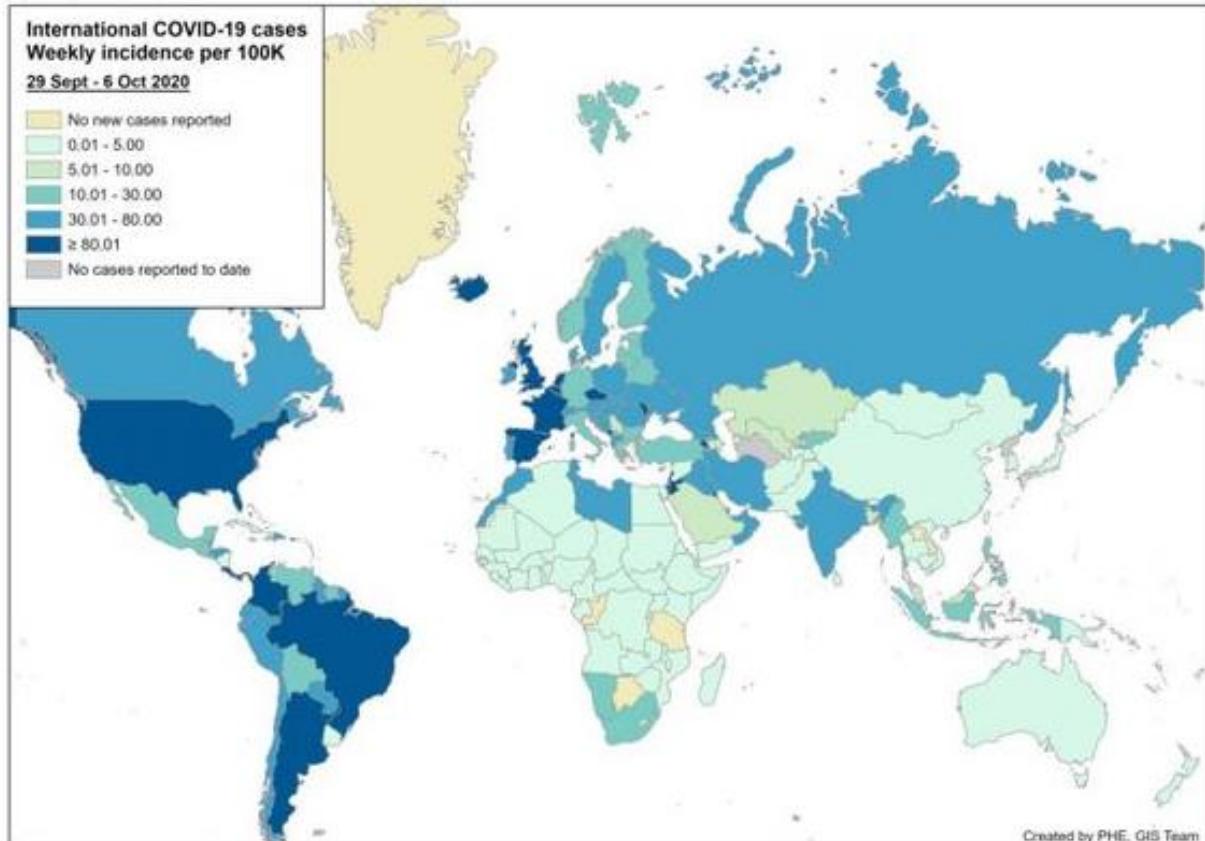
Covid-19 distribution

Malaria distribution
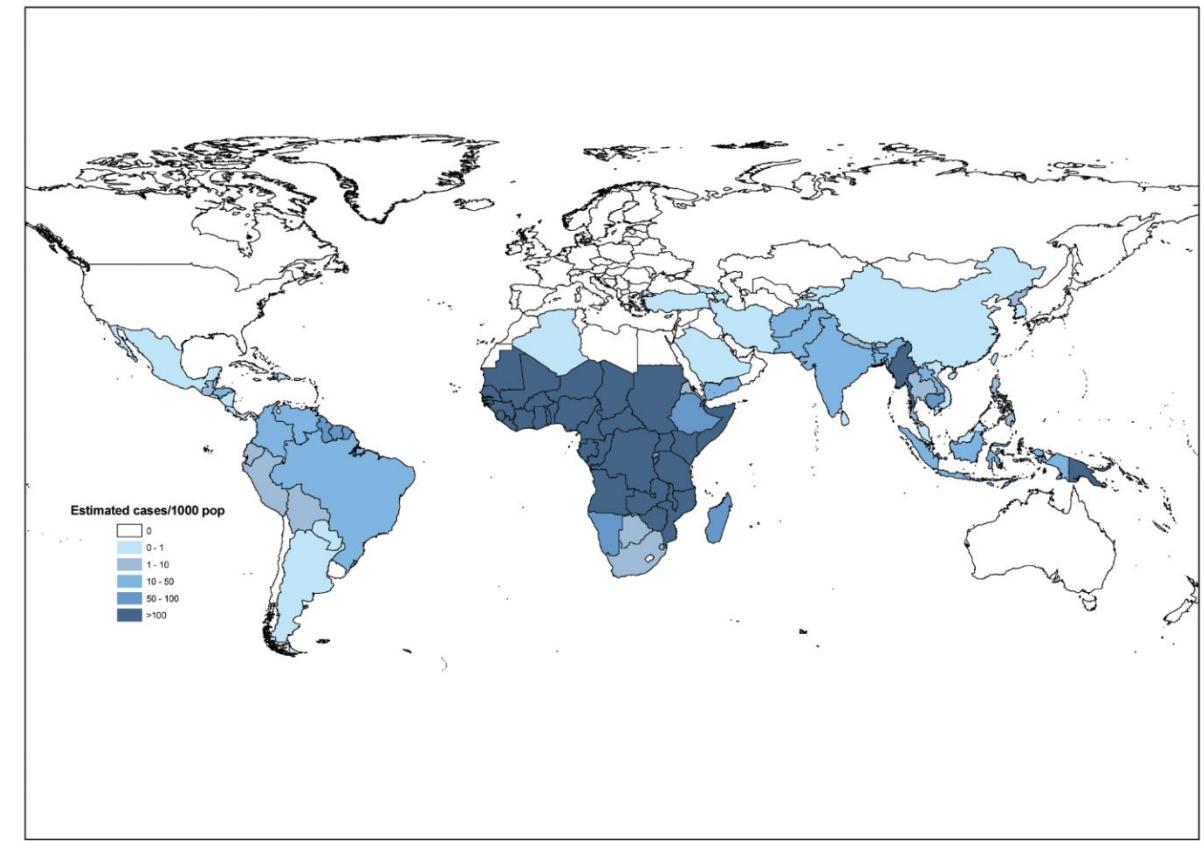
Background

- Despite the global spread of the SARS-CoV-2 virus, understanding of the epidemiology and clinical course of COVID-19 in sub-Saharan Africa is limited.

- The impact of COVID-19 on control of other infectious diseases and potential implications of any clinical interactions with these diseases remains a major public health concern.

- This study was conducted to
  - better characterise COVID-19 in a high malaria transmission setting
  - Determine the burden/describe the clinical impact of SARS-CoV-2 and malaria co-infection.

Methods

- **Study design:** Exploratory cohort study

- **Study sites:** Treatment centres in eight tertiary hospitals in Uganda

- **Sample size:** 600 polymerase chain reaction (PCR) confirmed COVID-19 patients

- **Timelines:** 15th April – 30th October 2020
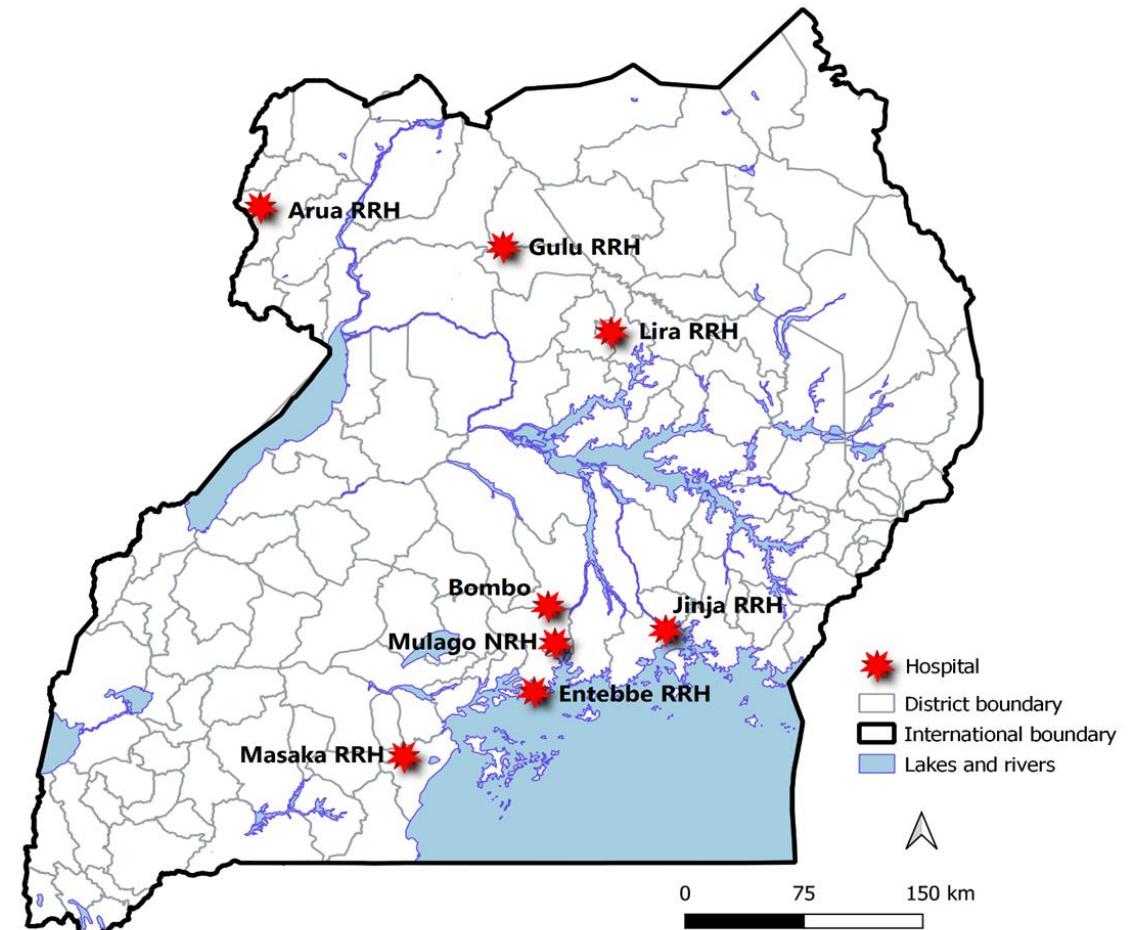
Methods

- Malaria diagnosis: rapid diagnostic tests, microcopy and molecular analysis (qPCR)

- Previous individual *Plasmodium falciparum* exposure measured using serologic responses to a panel of antigens associated with cumulative/recent exposure
  - apical membrane antigen-1 (AMA-1), merozoite surface protein1.19 (MSP1.19) and glutamate-rich protein (GLURP.R2)
  - reticulocyte-binding protein homologue (Rh2.2030), gametocyte exported protein (GEXP18) and Early transcribed membrane protein (Etramp5.Ag1)

- Clinical Labs: Complete blood count, liver and renal function tests, HIV test

- Markers of inflammation: C-Reactive protein (CRP), Interleukin (IL)-2, IL-6, IL-7, IL-8, IL-10, transforming growth factor beta (TGF-β), tumor necrosis factor (TNF-α)

- Laboratory personnel unaware of patients' clinical status to avoid potential bias

- Clinical management conducted according to Ministry of Health guidelines.

Study Profile

600 COVID-19 patients screened and enrolled

Three patients excluded due to significant missing information

597 patients included in the study analysis

70 *Plasmodium falciparum* positive

527 *Plasmodium falciparum* negative

597 assessed for outcomes
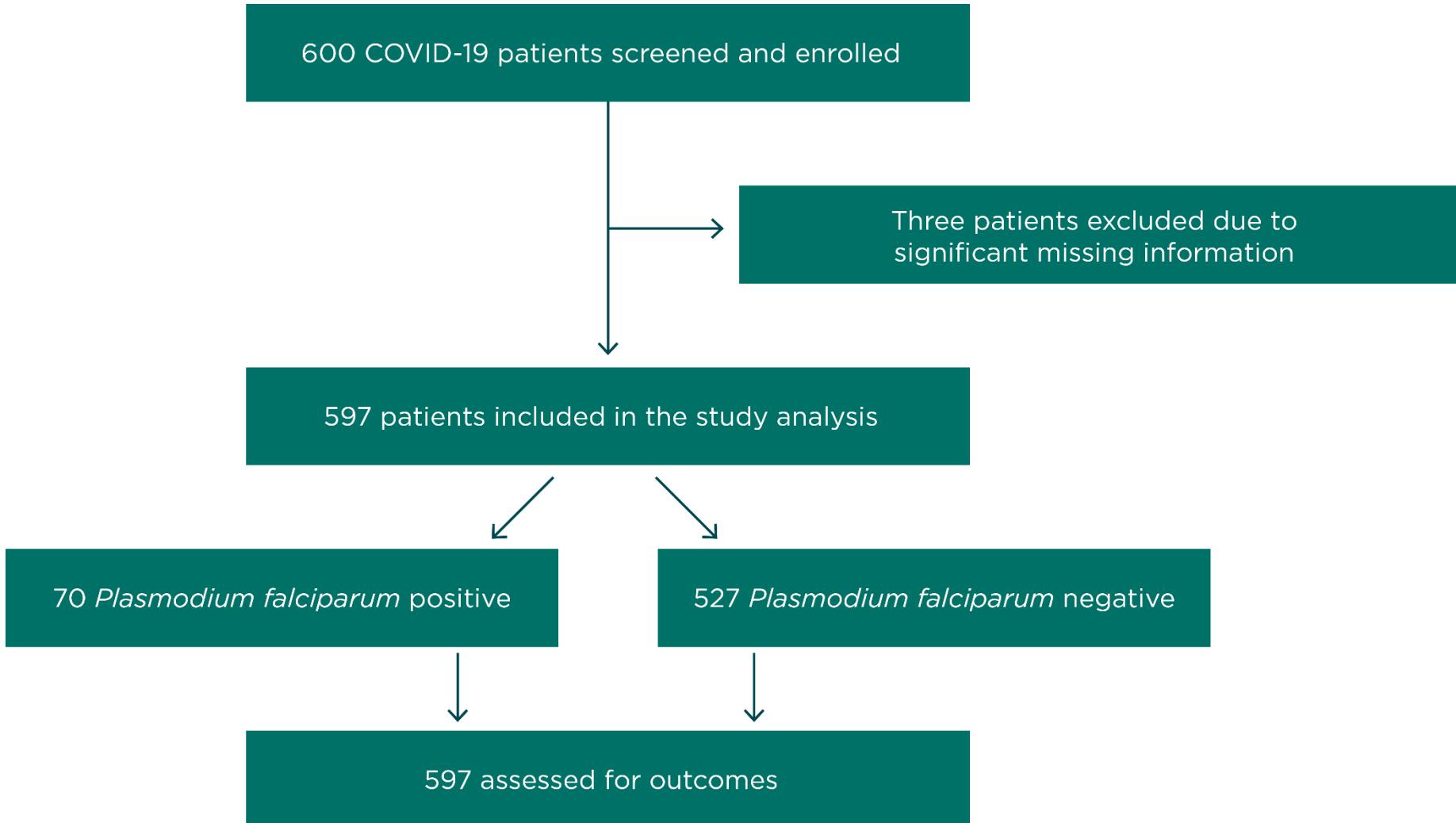
Baseline characteristics

Patient characteristic	Overall: (N = 597), n (%)
Age categories*	
0-20	23 (4)
21-40	355 (61)
41-60	163 (28)
>60	46 (8)
Age	
Mean (Standard deviation, SD)	38.2 (13)
Median (Interquartile range, IQR)	36 (28–47)
Ethnicity	
Black	587 (98)
Asian	10 (2)
Education	
None	26 (10)
Primary	76 (28)
Secondary	95 (35)
University	47 (17)
Other tertiary	28 (10)

Baseline characteristics

Patient characteristic	Overall: (N = 597), n (%)
Sex	
Male	502 (84)
Female	95 (16)
Occupation[+]	
Unemployed	10 (2)
Peasant farmer	12 (3)
Health worker	22 (5)
Armed forces	17 (4)
Professionals	41 (9)
Business	24 (5)
Truck driver	169 (38)
Other	160 (36)
Comorbidities	
Tuberculosis	3 (1)
Diabetes	49 (8)
Asthma/Chronic obstructive pulmonary disease (COPD)	9 (2)
Obesity	16 (3)
Heart disease	23 (4)
HIV	35 (6)
Hypertension	149 (25)

P. falciparum infection and previous malaria exposure

Malaria variable	n/N	Percentage (95% CI)
P. falciparum infection	70/597	12 (9.4–14.6)
P. falciparum infection by age		
0–20	5/23	22 (8.7–44.8)
21–40	36/365	10 (6.7–12.8)
41–60	20/163	12 (8.0–18.3)
>60	9/46	20 (10.2–34.1)
Previous malaria exposure		
Low	53/527	10 (7.8–12.9)
Medium	418/527	79 (75.6–82.6)
High	56/527	11 (8.3–13.6)

| Clinical parameter | Covid-19 patients by malaria infection and exposure category | | | | | | | |
| | | Current malaria infection | | | Previous malaria exposure | | | |
	Overall N = 597 (%)	Malaria N = 70 (%)	No malaria N = 527 (%)	Fisher's exact p-value	Low N = 53 (%)	Moderate N = 418 (%)	High N = 56 (%)	Fisher's exact p-value
Signs and symptoms								
Fever	121 (20)	15 (21)	106 (20)	0.752	17 (32)	92 (22)	6 (11)	**0.024**
Cough	198 (33)	19 (27)	179 (34)	0.342	27 (51)	150 (36)	13 (23)	**0.012**
Runny nose	129 (22)	11 (16)	118 (22)	0.220	9 (17)	103 (25)	10 (18)	0.298
Shortness of breath	98 (16)	13 (19)	85 (16)	0.605	23 (43)	71 (17)	3 (5)	**0.001**
Muscle pains	22 (4)	3 (4)	19 (4)	0.734	0 (0)	20 (5)	1 (2)	0.229
Confusion	12 (2)	4 (6)	8 (2)	**0.040**	1 (2)	9 (2)	0 (0)	0.715
Headache	112 (19)	16 (23)	96 (18)	0.329	13 (25)	81 (19)	11 (20)	0.665
Sore throat	49 (8)	2 (3)	47 (9)	0.103	5 (9)	38 (9)	4 (7)	0.924
Chest pain	84 (14)	8 (11)	76 (14)	0.586	17 (32)	61 (15)	4 (7)	**0.001**
Diarrhea	20 (3)	4 (6)	16 (3)	0.275	3 (6)	16 (4)	1 (2)	0.528
Vomiting	9 (2)	4 (6)	5 (1)	**0.014**	0 (0)	7 (2)	2 (4)	0.431
Fatigue	17 (3)	1 (1)	16 (3)	0.708	3 (6)	13 (3)	0 (0)	0.214
Red Eyes	4 (1)	0 (0)	4 (1)	1.000	1 (2)	3 (1)	0 (0)	0.389
Covid-19 Severity								
Asymptomatic	255 (43)	36 (51)	219 (42)		13 (25)	155 (37)	32 (57)	
Mild	233 (39)	18 (26)	215 (41)		17 (32)	183 (44)	20 (36)	
Moderate	45 (8)	6 (9)	38 (7)		7 (13)	35 (8)	1 (2)	
Severe/critical	64 (12)	10 (14)	54 (10)	0.084	16 (30)	45 (11)	3 (5)	**0.001**
Co-morbidities								
Tuberculosis	3 (1)	0 (0)	3 (1)	1.000	0 (0)	3 (1)	0 (0)	1.000
Diabetes	49 (8)	7 (10)	42 (8)	0.642	12 (23)	28 (7)	2 (4)	**0.001**
COPD	1 (0.2)	1 (1)	0 (0)	0.118	0 (0)	1 (0.2)	0 (0)	1.000
Asthma	8 (1)	0 (0)	8 (2)	1.000	4 (8)	4 (1%)	0 (0)	**0.014**
Obesity	16 (3)	3 (4)	13 (3)	0.421	5 (9)	10 (2)	1 (2)	**0.031**
Heart disease	23 (4)	2 (3)	21 (4)	1.000	7 (13)	14 (3)	0 (0)	**0.003**
HIV	35 (6)	5 (7)	30 (6)	0.586	1 (2)	21 (5)	4 (7)	0.429
Hypertension	149 (25)	11(16)	138(26)	0.057	20 (38)	100(24)	12 (21)	0.085
Clinical outcomes								
Discharged in good condition	479 (80)	57 (81)	422 (80)		32 (60)	334 (80)	48 (86)	
Discharged with sequelae	7 (1)	0 (0)	7(2)		0 (0)	6 (1)	0 (0)	
Admitted to ICU	31 (5)	4(6)	27(6)		7 (13)	22 (5)	2 (4)	
Died	9 (2)	2(3)	7(2)	0.558	2 (4)	7(2)	0 (0)	0.094

Association between *P. falciparum* infection, previous malaria exposure and COVID-19 clinical profiles among patients with no comorbidities

Clinical parameter	Overall N = 489 (%)	Covid-19 patients by malaria category						
		Current malaria infection			Previous malaria exposure			
		Malaria N = 55 (%)	No malaria N = 434 (%)	Fisher's exact p-value	Low N = 33 (%)	Medium N = 351 (%)	High N = 49 (%)	Fisher's exact p-value
Presence of signs and symptoms								
Fever	84 (17)	9 (16)	75 (17)	1.000	11 (33)	67 (19)	4 (8)	**0.019**
Cough	137 (28)	11 (20)	126 (29)	0.201	14 (42)	110 (31)	9 (18)	0.062
Runny nose	109 (22)	10 (18)	99 (23)	0.495	6 (18)	91(26)	8 (16)	0.275
Shortness of breath	46 (10)	6 (11)	40 (9)	0.624	9 (27)	34 (10)	2 (4)	**0.005**
Muscle pains	18 (4)	2 (4)	16 (4)	1.000	0 (0)	16 (5)	1 (2)	0.497
Confusion	5 (1)	2 (4)	3 (1)	0.098	1 (3)	3 (1)	0 (0)	0.328
Headache	92 (19)	13 (24)	79 (18)	0.356	8 (24)	73 (21)	8 (16)	0.670
Sore throat	41 (8)	2 (4)	39 (9)	0.295	3 (9)	35 (10)	3 (6)	0.777
Chest pain	45 (9)	3 (6)	42 (10)	0.456	8 (24)	34 (10)	2 (4)	**0.018**
Diarrhoea	13 (3)	4 (7)	9 (2)	**0.046**	1(3)	11 (3)	1 (2)	1.000
Vomiting	9 (2)	4 (7)	5 (1)	**0.011**	0 (0)	7 (2)	2 (4)	0.385
Fatigue	12(3)	1 (2)	11 (3)	1.000	2 (6)	9 (3)	0 (0)	0.240
Red eyes	3(1)	0 (0)	3 (1)	1.000	0 (0)	3 (1)	0 (0)	1.000
Clinical outcomes								
Favorable	444 (91)	51 (12)	393 (80)	0.805	31 (94)	316 (90)	45 (92)	0.903
Unfavorable	45 (9)	4 (1)	41 (8)		2 (6)	35 (10)	4 (8)	
Covid-19 severity								
Asymptomatic	230 (47)	31 (56)	199 (46)	0.095	11 (33)	143 (41)	30 (61)	**0.015**
Mild	206 (42)	16 (29)	190 (44)		13 (39)	167 (48)	17 (35)	
Moderate	24 (5)	5 (9)	19 (4)		3 (9)	19 (5)	1 (2)	
Severe/critical	29 (6)	3 (6)	26 (6)		6 (18)	22 (6)	1 (2)	

P. falciparum antibody responses and severity of Covid-19
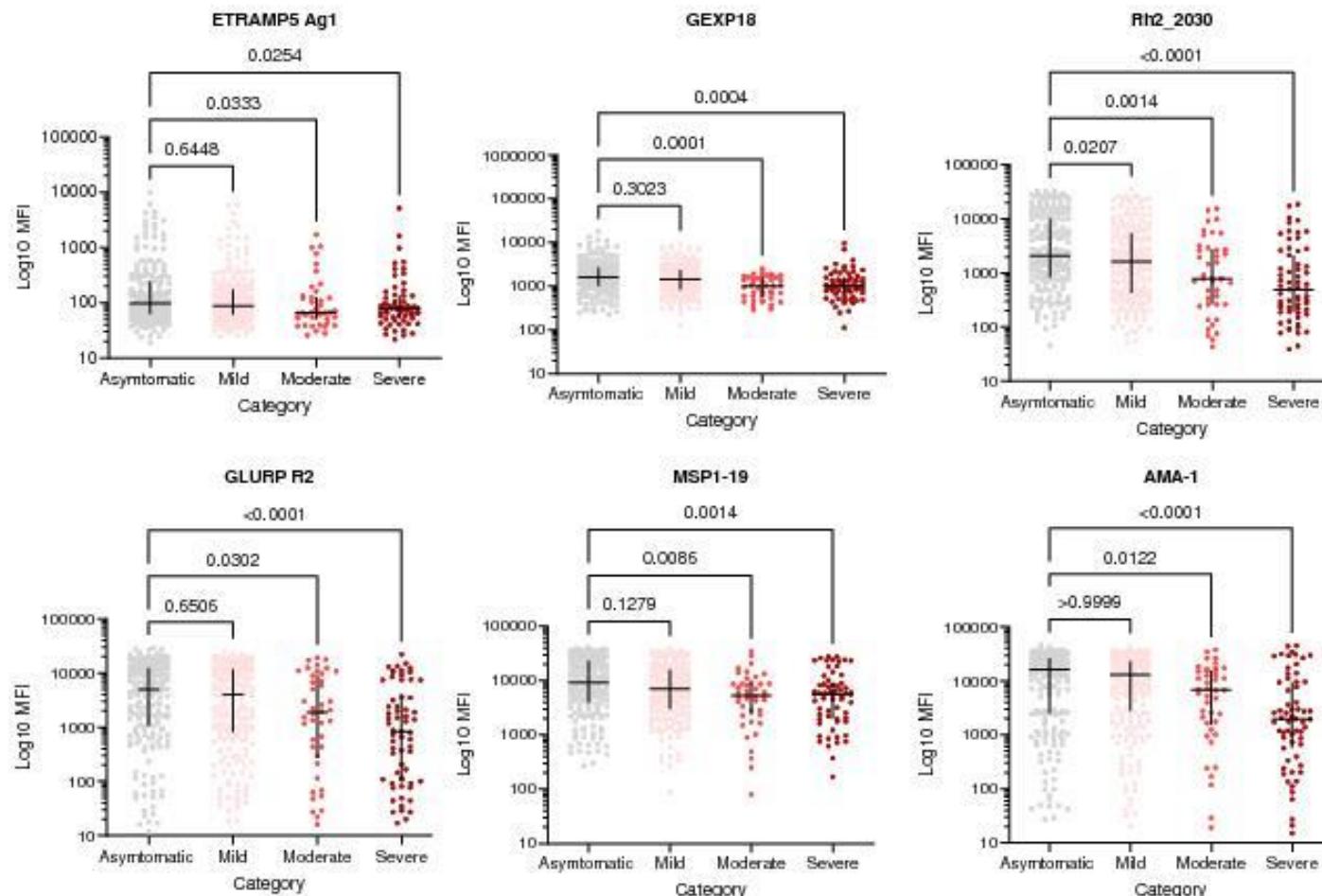
Cytokines, COVID-19 severity, malaria infection status and previous malaria exposure

Patient characteristics	Interleukin 2 (pg/ml)			Interleukin 6 (pg/ml)			Interleukin 7 (pg/ml)			Interleukin 8 (pg/ml)		
	Mean (SD)	Coef¶ (95% CI)	p-value	Mean (SD)	Coef¶ (95% CI)	p-value	Mean (SD)	Coef¶ (95% CI)	p-value	Mean (SD)	Coef¶ (95% CI)	p-value
Covid-19 severity												
Asymptomatic	19.6 (5.5)	1		1.5 (1.0)	1		6.4 (4.7)	1		53.1(115.0)	1	
Mild	19.6 (3.9)	-0.2 (-0.8–0.8)	0.956	1.7(1.8)	0.3 (-2.0–2.5)	0.820	6.6 (4.8)	0.4 (-0.8–1.6)	0.558	28.4 (83.1)	-24.7 (-43.2– -6.3)	0009
Moderate	19.2 (0)	-0.5 (-1.9–1.0)	0.522	10.8 (25.6)	9.3 (5.5–13.1)	0.001	12.4 (10.8)	6.5 (4.4–8.5)	0.001	58.1 (89.5)	4.9 (-27.0–36.9)	0.76
Severe	19.2 (0)	-0.5 (-1.7–0.7)	0.454	13.0 (27.4)	11.5 (8.2–14.7)	0.001	13.9 (10.8)	7.7 (5.9–7.1)	0.001	52.2 (58.5)	-1.0 (-28.0–26.1)	0.94
Malaria infection												
Negative	19.6 (4.5)	1		3.9 (12.9)	1		7.9 (7.1)	1		42.5 (94.2)	1	
Positive	19.2 (0)	-0.4 (-1.5–0.7)	0.478	2.3 (3.3)	-1.5 (-4.7–1.6)	0.337	7.7 (5.7)	-0.2 (-2.0–1.6)	0.852	42.1 (104.5)	0.6 (-24.3–25.6)	0.962
Previous malaria												
Low	19.8 (4.4)	1		3.6 (5.8)	1		10.8 (9.5)	1		30.3 (34.6)	1	
Medium	19.6 (4.6)	-0.2 (-1.4–1.0)	0.730	4.0 (13.6)	0.4 (-3.1–4.0)	0.816	7.9 (7.9)	-2.9 (-4.9– -0.9)	0.004	41.9 (41.9)	11.6 (-13.7–36.9)	0.368
High	19.2 (0)	-0.6 (-2.2–1.0)	0.471	2.1 (3.4)	-1.5 (-6.1–3.1)	0.526	5.2 (3.4)	-5.6 (-8.2– -3.0)	0.001	41.4 (41.4)	11.0 (-22.0–44.1)	0.512
Clinical outcomes												
Good outcome	19.6 (4.5)	1		2.8 (9.4)	1		7.6 (6.7)	1		40.0 (97.1)	1	
Unfavorable outcome*	19.2 (0)	-0.4 (-3.0–2.2)	0.759	20.1 (22.6)	17.3 (11.2–23.3)	0.001	9.1 (8.3)	1.4 (-2.5–5.3)	0.475	77.1 (81.8)	37.0 (-18.6–92.6)	0.191

Cytokines, COVID-19 severity, malaria infection status and previous malaria exposure

Patient characteristics	Cytokine profiles								
	TNF-α (pg/ml)			TGF-β1 (pg/ml)			Interleukin 10 (pg/ml)		
	Mean (SD)	Coef¶ (95% CI)	p-value	Mean (SD)	Coef¶ (95% CI)	p-value	Mean (SD)	Coef¶ (95% CI)	p-value
Covid-19 severity									
Asymptomatic	4.8 (1.2)	1		162457 (105430.3)			9.2 (75.2)	1	
Mild	4.8 (1.5)	0.1(-0.3–0.3)	0.829	154715 (94974.1)	-7741.8 (-27887.2–12403.6)	0.451	11.9 (85.2)	2.7 (-18–23.8)	0.801
Moderate	4.9 (0.6)	0.1(-0.4–0.6)	0.678	173140 (95712.1)	10682.8 (-23960–59893.5)	0.545	6.8 (15.6)	-2.4 (-38.6–33.8)	0.897
Severe	5.4 (2.5)	0.6(0.2–1.0)	0.004	192485 (145064.7)	30028.2 (162.9–59893.5)	0.049	37.8 (234.9)	28.6 (-2.4–59.5)	0.070
Malaria infection									
Negative	4.8 (1.1)	1		164147 (104383.2)	1		14.1 (115.4)	1	
Positive	5.4 (3.1)	0.6 (0.3–1.0)	0.001	160068 (121007.5)	-4079.3 (-31759–23601.3)	0.772	7.6 (18.1)	-6.5 (-34–21.7)	0.650
Previous malaria									
Low	4.7 (0.7)	1		201746 (130924.9)	1		5.8 (10.9)	1	
Moderate	4.8 (1.3)	0.1 (-0.3–0.5)	0.641	166932 (105540.2)	-34813.9 (-65344.4– -4283.4)	0.026	15.9 (123.3)	10.1 (-21.4–41.7)	0.528
High	5.1 (2.5)	0.4 (-0.2–0.9)	0.169	116307 (76013.8)	-50625 (-85439.2– -45470.8)	0.001	4.4 (8.1)	-1.4 (-42–40.0)	0.948
Clinical outcomes									
Good outcome	4.8 (1.4)	1		160808 (100811.4)	1		10.9 (77.6)	1	
Unfavorable outcome*	5.8 (2.2)	0.9 (0.1–1.8)	0.029	174395 (137530.8)	13586.7 (-44667–71840)	0.647	160.0 (224.3)	149.1(84.5–213.6)	0.001

Cytokines, Covid-19 severity, malaria infection status and previous malaria exposure

- No differences in cytokine levels among patients with or without malaria except for TNF-α which was higher in malaria positive patients.

- IL-6, IL-7, TNF-α and TGF-β1 levels were higher among patients with more severe Covid-19 presentation.

- IL-6 and IL-10 were higher among patients with unfavorable outcomes.

- No significant elevation in IL-2 was observed in this patient population.

Clinical factors associated with unfavorable outcome among Covid-19 patients

Patient attribute	Covid-19 patient outcomes		Crude odds ratio (OR) (95% CI)	Adjusted OR (95% CI)	p-value
	Unfavorable outcome* N = 73 (%)	Discharged in good condition N = 524 (%)			
Age categories					
0–20	2 (3)	21 (4)	1	1	
21–40	32 (44)	323 (62)	1.0(0.2–4.6)	1.8(0.2–14.0)	0.584
41–60	18 (25)	145 (28)	1.3(0.3–6.0)	1.9(0.2–15.8)	0.534
>60	19 (26)	27 (5)	7.4(1.5–35.3)	8.7(1.0–75.5)	0.049
Sex					
Male	59 (81)	443 (85)	1	1	
Female	14 (19)	81 (16)	1.3 (0.7–2.4)	0.9 (0.4–1.9)	0.820
Current Malaria infection					
Negative	65 (89)	462 (88)	1	1	
Positive	8 (11)	62 (12)	0.9 (0.4–2.0)	0.8 (0.3–2.0)	0.663
Previous malaria exposure					
Moderate	53 (73)	365 (70)	1	1	
Low	10 (14)	43 (8)	1.6 (0.8–3.4)	1.1 (0.5–2.5)	0.840
High	6 (8)	50 (10)	0.8 (0.3–2.0)	1.0 (0.4–2.6)	0.998
Diabetes					
No	57 (78)	488 (93)	1	1	
Yes	16 (22)	33 (6)	4.2 (2.2–8.0)	2.1 (0.9–5.0)	0.077
Heart disease					
No	64 (88)	501 (96)	1	1	
Yes	7 (10)	16 (3)	0.3 (0.1–0.7)	0.5 (0.2–1.5)	0.217

Conclusions

- Prevalence of *P. falciparum* infection among hospitalised COVID-19 patients in this population was 12 percent.

- Though COVID-19 patients with *P. falciparum* infection had a higher frequency of confusion and vomiting, co-infection with malaria did not seem deleterious.

- The association of low previous malaria exposure with severe/critical COVID-19 and adverse outcomes requires further study.

- These preliminary observations highlight the importance of understanding the potential clinical and therapeutic implications of such overlapping co-infections in similar settings.

Acknowledgments

Thank you

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