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Malaria and COVID-19 co-infection: a symptom diagnostic challenge in a malaria endemic setting

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ABSTRACT:

— ***Objective:*** To determine the prevalence and risk factors for malaria and COVID-19 co-infection.

— ***Patients and methods:*** A total of 135 COVID-19 positive patients were consecutively recruited from the Infectious Diseases Hospital, Olodo, Ibadan, Oyo State. Nasopharyngeal and oropharyngeal swab samples were obtained during hospitalization and tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) using the BGI SARS-Cov-2 kit (China). Blood was also obtained by needle prick and malaria tests were performed using the SD BIOLINE Malaria Ag P.f/Pan test. Risk factors were entered into individual case investigation forms.

— ***Results:*** Malaria and COVID-19 co-infection rate was 7%. The predominant clinical manifestation was fever (28.1%) and the study showed that COVID-19 and malaria co-infection was associated with increased odds of fever compared to COVID-19 mono-infection (p-value=0.415, OR=4.960). Significant risk factors for malaria/COVID-19 are age of participants (p= 0.000) and CT values for by SARS-Cov2 RT-PCR (p=0.013). Fever is a common symptom in either malaria or COVID-19 infection thus posing a diagnostic challenge. Proper risk assessment of febrile patients and laboratory evaluation for COVID-19 and/or malaria is a prerequisite for appropriate distinction.

— ***Keywords:*** Malaria, COVID-19, Symptom.

INTRODUCTION

The Coronavirus disease (COVID-19) pandemic has continued to spread rapidly across continents in unprecedented proportions, extending to 213 countries and territories[1]. As of April27, 2021, there have been149,123,453 confirmed cases of COVID-19 reported worldwide with Africa accounting for 4,554,806 cases[2]. The four African countries reporting most cases are South Africa (1,576,320), Morocco (509,972), Ethiopia (254,944) and Nigeria (164,756)[2].

Malaria is a widespread endemic disease in most African countries with an estimated 230 million cases and approximately 430,000 annual deaths[3]. The additional threat of COVID-19 has impacted negatively on the already weak healthcare system by contributing to the existing burden of infectious diseases plaguing sub-Saharan Africa, including Malaria, Human immunodeficiency virus (HIV) and Tuberculosis infections[4].

Non-specific manifestations of COVID-19 such as fever, headache, tiredness, and muscle pains are not

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clearly distinct from malaria symptoms, particularly in malaria endemic settings[5]. COVID-19 diagnosis is based on a positive RT-PCR test result for the presence of the SARS-Cov-2 virus regardless absence of symptoms[6]. Although COVID-19 testing is currently free in Nigeria, the test is not readily available and accessible in all the states. Contrastingly, validated rapid diagnostic tests (RDTs) and microscopic examination of thin and thick blood smears are readily accessible for malaria diagnosis nationwide.

Relatively mild and non-specific clinical manifestations in most African countries coupled with the lower mortality have further fueled the infodemic that malaria is being infrequently misdiagnosed as COVID-19. At present, it is expected that much attention is paid towards COVID-19 due to the high level of alertness at health and medical care centers, both across the country and the globe[7]. Hence, febrile people might be wrongly assumed to have COVID-19 or conversely, febrile patients might get tested or treated for malaria when they actually have COVID-19 infection. Regardless, both scenarios may have public health implications as a single missed case of COVID-19 has the potential to transmit to up to 3.58 susceptible individuals, while untreated malaria on the other hand could be associated with further complications among the most vulnerable populations[8].

As the transition from dry to rainy season begins in malaria endemic countries, health care workers and community members come across an important challenge of identifying positive cases of COVID-19 infection[3,9]. This potentially has serious negative implications on early seeking for COVID-19 testing, consequent case management, isolation and contact tracing. There is a dearth of information on the epidemiology of malaria and COVID-19 co-infection hence, it is unclear whether potential immunomodulatory effect of *Plasmodium*infection will be beneficial or harmful when there is co-infection with the SARS-CoV-2 virus[10]. As with COVID-19, cellular immune responses in malaria involving the cytokine cascade must be carefully regulated to achieve a protective response without causing an adverse impact on the host.

Previous studies[11,12] in malaria-endemic regions have shown that similar to COVID-19, severe manifestations of malaria are often due to excessive host pro-inflammatory responses. This suggests that a potential co-infection of malaria and COVID-19 might also lead to an excess pro-inflammatory response which could result in an increased disease severity and poor prognosis[10].

Global efforts on malaria control have resulted in a significant reduction in the global burden of malaria, with 11 countries achieving malaria elimination. However, these gains will be threatened by the rapid spread of COVID-19, as COVID-19 and malaria transmission models have shown that disruption of malaria prevention activities, with consequent reduction in the malaria case management and delays in the long-lasting insecticide treated nets (LLIN) campaigns, could result in 81000 additional deaths[13,14].

Here, we assessed the burden of COVID-19 and malaria co-infection and the potential risk factors among newly diagnosed COVID-19 patients in an isolation center.

PATIENTS AND METHODS

A total of 135 COVID-19 positive patients were consecutively recruited from the Infectious Diseases Centre, Olodo, Ibadan, Oyo State. Ethics approval was sought and received from the Oyo State Ethics Board. Additional nasopharyngeal and oropharyngeal samples were obtained during hospitalization and tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) using the BGI SARS-Cov-2 kit (China) which detects the Open Reading Frame 1ab gene (ORF1ab) of SARS-Cov2 with a cut-off Cycle Threshold (CT) value of 38[15]. Blood was also obtained by needle prick and malaria tests were performed using the SD BIOLINE Malaria Ag P.f/Pan test a rapid, qualitative, and differential test for the detection of histidine-rich protein II (HRP-II) antigen of *Plasmodium falciparum* and common Plasmodium lactate dehydrogenase (pLDH) of Plasmodium species in human whole blood. Relevant Biodata of each participant were entered into individual case investigation forms.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version. 22.0 (IBM Corp, Armonk, NY, USA). Descriptive analysis was used to obtain the averageage and standard deviation of respondents, frequency distribution for the demographic features, co-morbidity, CT range and the clinical characteristics of COVID-19 patients. Charts were also used where appropriate. Inferential statistics were finally carried out to establish relationships using the chi-square test and the binary logistic regression to determine the odd ratios of the risk factors associated with COVID-19 and malaria co-infection.

RESULTS

The averageage of the study participants is 35.8±13.6. The majority (34.1%) were within the age group of 20-29 years old, while theminority (4.4%) was within the age group 10-19 years. All participants were recruited within a period of four months spanningApril to July 2020. Participants were predominantly males (67.4%) giving a male: female ratio of 2.2:1. Healthcare workers were the least frequent (4.4%) while the majority was another category of workers includingtailors, carpenters, traders, and farmers. Participants were predominantly (65.2%) Christians, and the majority (85.2%) were resident in Ibadan, Oyo State (Table 1).

Nine (7%) of the COVID-19 positive participants were also co-infected with malaria. The major clinical symptom the participants experienced was fever (28.1%)

Table 1. Socio-demographic characteristics of participants (n=135).

Variable	Frequency	Percentage(%)
Age group (years)		
10-19	6	4.4
20-29	46	34.1
30-39	43	31.9
40-49	14	10.4
50-59	16	11.9
60 and above	10	7.4
Total	135	100.0
Gender		
Female	44	32.6
Male	91	67.4
Total	135	100.0
Religion		
Christianity	88	65.2
Islam	47	34.8
Total	135	100.0
Occupation		
Civil servants	13	9.7
Healthcare workers	6	4.4
Student	8	5.9
Media practitioner	48	35.6
Unemployed	8	5.9
Others	52	38.5
Total	135	
Residence		
Within Ibadan	115	85.2
Outside Ibadan	20	14.8
Total	135	

followed by headache (24.1%), cough (16.3%) and anosmia (14.8%). Other symptoms are shown in Figure 1. The median CT value was 32.41, while the Interquartile CT range was 6.22. The CT levels varied significantly (p=0.013) with malaria and COVID-19 co-infection (Table 2). Most of the participants (77.3%) had no pre-existing co-morbidity, while 12.9% of them had underlying hypertension and other cardiovascular diseases. There was no significant relationship between co-morbidities and malaria/COVID-19 co-infection (Table 3).

Table 4 shows that with respect to religion, the participants (Christians) are 1.237 (p=0.692) times more likely to be co-infected with COVID-19 and malaria, while with age, they are 2.014 times (p=0.000) more likely to be infected. Gender and occupation of the respondents, although not significant (p=0.508 and p=0.856, respectively), showed that choice of occupation and gender category are 1.093 times less likely or 1.110 times more likely to be associated with malaria and COVID-19 co-infection.

Although none of the observed COVID-19 symptoms showed any statistical significance, the likelihood of the participants varied as obtained from their odds ratios. The presence of fever among participants suggests that the individual is 4.96 times more likely to suffer from malaria/COVID-19 co-infection, while headache and sore throat are symptoms that are 3.95 and 1.24 times less, respectively, to be associated with malaria/COVID-19 co-infection. Difficulty in breathing is associated with 1.565 times more likelihood of co-infection, while chest pain is associated with a higher likelihood of 3.99 times. Anosmia and ageusia have been calculated to be1.093 and 2.124 times more associated with malaria/COVID-19 co-infection. Cough indicates that participants are 4.207 times more likely to be co-infected with malaria/COVID-19, while malaise and vomiting are symptoms which indicate 3.815 and 2.197 times more likelihood to be co-infected with malaria and COVID-19 (Table 5).

DISCUSSION

The malaria and COVID-19 co-infection rate in the current study is 7%. This is not surprising as the rates of malaria are usually lower during the dry season periods which coincide with the time of the present study. Contrastingly, it has been postulated that with the rapid trans-

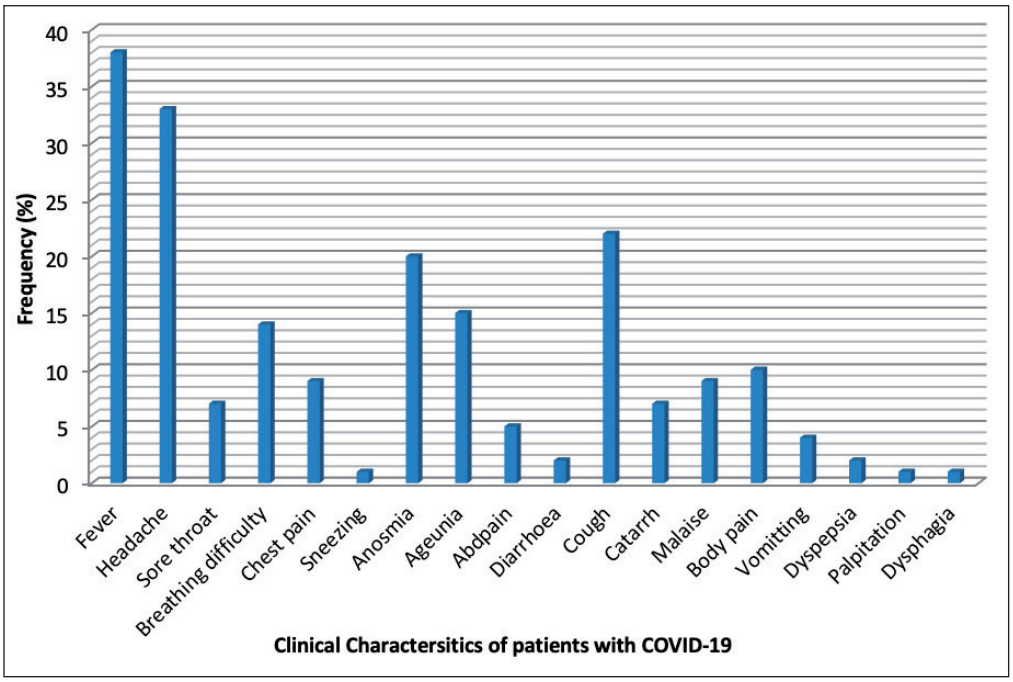

Figure 1. Clinical characteristics of COVID-19.

Table 2. Relationship between cycle threshold and malaria/COVID-19 co-infection.

		co-infection status				
		No	Yes	Total	chi square	*p*-value
< CT category	Less or equal 20	19(14.4%)	5(3.58%)	24(18.2%)	12.64	0.013*
	21-25	10(7.6%)	4(3.0%)	14(10.6%)		
	26-30	32(24.2%)	11(8.3%)	43(32.6%)		
	31-35	29(22.0%)	1(0.8%)	30(22.7%)		
	Greater than 35	21(15.9%)	0(0%)	21(15.9%)		
	Total	111(84.1%)	21(15.69%)	132(100.0%)		

*There is a statistical significance (0.013) between CT and the co-infection status of respondents.

Table 3. Relationship between co-morbidities and Malaria/COVID-19 co-infection.

		Malaria				
		No	Yes	Total	chi square	*p*-value
Co-morbidity	Respiratory system (COPD)	1(0.8%)	0(0%)	1(0.8%)	1.827	0.767
	Peptic ulcer disease	2(1.5%)	0(0%)	2(1.5%)		
	Hypertension and other cardiovascular diseases	17(12.9%)	0(0%)	17(12.9%)		
	Sickle cell disease	1 (0.8%))	0(0.0%)	1(0.8%)		
	No co-morbidity	102(77.3%)	9(6.8%)	111 (84.1%)		
Total		123(93.2%)	9(6.8%)	132(100.0%)		

*There is a statistical significance (0.013) between CT and the co-infection status of respondents.

mission of SARS-CoV-2, more people in LMICs, particularly in Africa, will be co-infected with the SARS-CoV-2 virus and Plasmodium parasites or with other of the neglected tropical diseases (NTD) pathogens[15].

Both COVID-19 and malaria are known to elicit cellular immune responses, mainly those of the cytokine cascade[16]. Severe manifestations of malaria are often due to the excessive pro-inflammatory responses, as inflam-

Table 4. Relationship between socio-demographic characteristics and COVID-19/malaria co-infection.

			95% C.I.for OR	
Variable	P-value	OR	Lower	Upper
Religion	0.692	1.237	0.432	3.543
Age	0.000	2.014	1.399	2.898
Occupation	0.508	0.915	0.703	1.191
Sex	0.856	1.110	0.360	3.419
Total		123(93.2%)	9(6.8%)	132(100.0%)

Table 5. Relationship between clinical symptoms and COVID-19/Malaria co-infection.

			95% C.I.for OR	
Variable	P-value	OR	Lower	Upper
Fever	0.154	4.960	0.547	44.956
Headache	0.272	0.253	0.022	2.947
Sore throat	0.887	0.809	0.043	15.317
Breathingdifficulty	0.802	1.565	0.047	51.879
Chestpain	0.284	3.990	0.317	50.197
Anosmia	0.967	1.093	0.016	74.662
Ageunia	0.745	2.124	0.023	199.592
Cough	0.088	4.207	0.809	21.880
Malaise	0.586	3.815	0.031	473.372
Vomiting	0.735	2.197	0.023	210.110

matory cytokine–mediated increased capillary permeability or endothelial damage has been linked to acute respiratory distress syndrome (ARDS) in COVID-19[17-19]. The aforementioned observation could suggest that malaria /COVID-19 co-infection will also lead to excess pro-inflammatory responses, which might further result in more severe manifestations and poor prognosis.

Common symptoms of infection with SARS-CoV-2 include fever, cough, difficulty in breathing, chills, myalgia, headache, sore throat, and loss of taste or smell[20,21]. The predominant symptom observed among participants in this study was fever. A previous meta-analysis study of solely COVID-19 patients had reported fever (88%) as the most common symptom, followed by dry cough (68%)[22]. As fever is also a common symptom of malaria, the overlap of COVID-19 and malaria symptoms could delay COVID-19 diagnosis or commencement of malaria treatment. Both situations constitute a challenge to the infected person and the community at large.

There is currently no specific treatment available for COVID-19, however the search for host directed therapies has led to the use of repurposed drugs including antiretroviral and antimalarial drugs such as chloroquine and hydroxychloroquine[23,24]. All the participants of this study were treated for COVID-19 with either chloroquine or hydroxychloroquine and all of them survived and were discharged within an average of 7 days of admission to the hospital. The potential dual synergistic effect of this therapy against SARS-COV-2 and Plasmodium parasites will require further considerations.

The Cycle threshold (CT) is the cycle number when the sample fluorescence exceeds a chosen threshold, above the calculated background fluorescence[25]. Studies[26,27] have reported a significant association between CT value or viral loads and disease severity among hospitalized COVID-19 patients. The CT values of the COVID-19 and malaria co-infected patients were within moderate ranges of 26.29-33.10. Malaria-induced immunomodulation has been shown to be protective against severe manifestations of some respiratory viruses[28]. Hence Plasmodium–SARS-CoV-2 co-infection might potentially ameliorate the clinical manifestations of COVID-19 thus delaying the time until seeking appropriate health intervention. Consequently, this might result in further spread of the virus within the community. Further studies are required to assess the possibility of whether malaria infection might worsen COVID-19, or *vice versa*.

The most common pre-existing morbidity among participants was hypertension and other cardiovascular diseases. Similar observation of hypertension as the predominant co-morbidity has been reported in previous studies[29,30]. A meta-analysis of 1,576 patients in China showed that all co-morbidities, except diabetes and obesity were associated with increased risk of severe disease[31]. However, here we showed no significant relationship between pre-existing co-morbidities and malaria/COVID-19 co-infection.

Most of the participants were within the age group of 20-29 years and the age factor was found to be significantly associated with malaria/COVID-19 co-infection. In malaria endemic region, susceptibility to malaria differs by age as younger children are more vulnerable to malaria infections[32]. Our study showed that 20-29 years old participants are 1.237 times more likely to be co-infected with COVID-19 and malaria. How age-related susceptibility to COVID-19 plays out in Africa is still largely unknown as many children and younger adults are already immunologically stimulated by several infections in addition to malaria[33]. Hence, it remains still unknown whether this underlying infection will alter susceptibility to or severity of COVID-19 infection among these populations.

CONCLUSIONS

Surveillance activities in addition to additional testing for malaria could help determine rates of co-infection and compare severity of outcomes by infection status. There might be a need to integrate malaria screening into COVID-19 surveillance to avert reversal of the gains achieved with malaria control programs.

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