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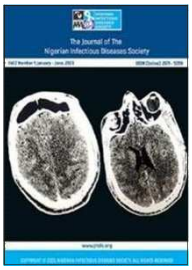

Original Article

Prevalence of Malaria and Typhoid Fever in COVID-19 Patients in Kaduna State, Nigeria

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Abstract

Background: While taking great measures to prevent COVID-19, other potentially fatal and endemic diseases with similar clinical presentation, such as malaria, typhoid fever, HIV, tuberculosis, Lassa fever, among others should not be ignored. The study aimed to determine the incidence of malaria and typhoid fever co-infection in patients with COVID-19.

Methods: Blood samples were collected from 770 participants who presented to the four screening sites between July and September 2020 at four of the Local Government Areas (LGA) within the Kaduna metropolis, for typhoid and malaria screening. Swab samples was taken from the nares, posterior pharynx, and tonsillar areas of eligible participants for COVID-19 molecular analysis by real-time PCR using QIAamp® Viral RNA Mini Kit (Qiagen, Germany) for extraction and the SARS-CoV-2 DaAn Gene primer kits, for detection (Sun Yat-sen University, Ghangzhou, China). Data analysis was carried out using the Statistical Package for the Social Sciences (IBM SPSS) version 23, by computing frequencies, proportions, and Chi square ($\chi 2$). Statistical significance was determined using p-value <0.05.

Results: The incidence of COVID-19 was 19.6%, malaria was 11.7%, and typhoid fever was 25.8%. COVID-19/typhoid co-infection was 27.8%, COVID-19/malaria co-infection was 13.9%, and typhoid fever and malaria had a 2.9% co-infection rate.

Conclusions: With acknowledging the potential limitations of typhoid serological tests, typhoid seropositivity and typhoid/COVID-19 co-infection rates were high in our population. Health-care packages that can be utilized simultaneously and targeted at screening for different febrile diseases, which may be co-existing with COVID-19 infection within the same patient should be explored in regions with high endemic of infectious diseases.

Key words: COVID-19, Epidemiology, Malaria, Typhoid fever, Kaduna

INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 has rapidly spread to all continents around the world. In Africa, compared to other regions, COVID-19 has been relatively milder in severity, but has the potential to trigger other larger crises in the region due to the vulnerability of health and economic systems, coupled with the high burden of malnutrition, human immunodeficiency virus (HIV), tuberculosis (TB), and other endemic diseases including malaria.[1,2]

The spread of COVID-19 infection to Africa had been quite slow or reasons yet to be elucidated, yet various reasons have been considered to explain such reasons, one is the effect of the high malaria burden and also the tropical climatic conditions of sub-Saharan Africa, on the virus.[3] In comparison, the WHO malaria report indicates that there were an estimated 228 million cases and 405,000 deaths due to malaria globally in 2018, as compared with the 241 million and 627,000 deaths seen in 2022, majority of which were from the Africa region for both years. [4] This could be as result of shift of attention from the malaria intervention globally to COVID-19 pandemic.

Some acute conditions share some of the more recognisable symptoms with COVID-19 such as: fever, difficulty in breathing, fatigue, and headaches of acute onset. Thus, a malaria case for instance may be misclassified as COVID-19 if symptoms alone are used to define a case during the pandemic and vice versa. Malaria symptoms appear within 10-15 days after an infective bite; multi-organ failure is a common complication in severe cases among adults while respiratory distress is often encountered in children with malaria, imitating what is usually reported in patients with COVID-19.[5]

Malaria is a widespread endemic disease; that causes illness in approximately 230 million people and kills approximately 430,000 people each year[4]. Over the past two decades, Ministries of Health (MoHs), National Malaria Control Programmes (NMCPs), Health Facilities and Community Health Workers (CHWs) have done substantial work to dramatically control the disease, and progress is tangible and visible in communities.[6, 7]

While taking great measures to prevent COVID-19, it is essential that other potentially fatal diseases, such as Malaria, Enteric fever, HIV, Tuberculosis, Lassa fever, et cetera, are not ignored. The COVID-19 pandemic could be devastating on its own but this devastation will be substantially amplified if the response undermines the provision of life-saving services for other preventable and/or treatable diseases.

Several febrile illnesses share quite several symptoms with COVID-19 and a lot of these infections are missed because of the current focus on the COVID-19 pandemic and its prevention and containment.[9]

This can potentially compromise progress towards diagnosis and management of other febrile illnesses of equal public health significance. In Sub-Saharan Africa with a huge burden of infectious diseases resulting to febrile illnesses, there is the tendency of missing some infections, thereby increasing the morbidity and mortality accruing to them[9]. This study aimed to determine the co-infection rate of febrile illnesses such as malaria and typhoid fever common in this community in COVID-19 infected patients. It is necessary that while the active testing for COVID -19 is on-going, the diagnosis and management of other causes of febrile illnesses are not impeded.

MATERIALS AND METHODS

Study Area

The study was conducted in the four of the LGAs within the metropolis (Kaduna North, Kaduna South, Chikun, and Igabi) of Kaduna State, which is located in the northern part of Nigeria's high plains, with an estimated population of approximately 2,119,700 for the four LGAs within the metropolis namely Igabi, Kaduna North; Kaduna South, Chikun[10].

Study Design/Sample Size

The cross-sectional study was conducted among all patients that presented within 3 months to state-established screening sites during the COVID-19 pandemic (July-Sept 2020). Consenting individuals with or without fever presenting for COVID-19 testing at community screening sites across these four LGAs were included in the study. Non-consenting individuals and persons who had taken or were on antimalarial or antimicrobial agents two weeks before, and, those who were re-testing for COVID-19 after a previously positive test were excluded. A total of 770 persons consented to participate in the survey.

Sample Collection and Laboratory Analysis

A structured interviewer-administered questionnaire was used to obtain data from all consenting participants. Data on demography which include, age and sex of the participants, symptoms of febrile illness and other factors related to COVID-19 were obtained by the research assistants. Thereafter, 5 mL blood sample was collected from each participant using an EDTA vacutainer and needle. The blood sample was then transported to the medical microbiology laboratory at Barau Dikko Teaching Hospital for screening for malaria fever and typhoid fever using rapid test kits. The kit used for typhoid screening was TyphyRapid®, a lateral flow immunochromatographic test which detects specific IgM S. Typhi antibodies, using specific S. Typhi antigen immobilized on a membrane strip, manufactured by Bio-diagnostics Research Inc., Malaysia and that for malaria screening was SD BIO LINE®, a one-step immunochromatographic test for the qualitative detection of Histidine-rich protein II (HRP-II) antigen of the malaria *Plasmodium falciparum*, manufactured by Standards Diagnostics inc., Republic of Korea with sensitivity 99.7 % and specificity 99.3 %.

Analysis was done per manufacturer's instruction.

Each participant had a Dacron swab inserted through the nostril parallel to the palate until resistance is encountered. The swab was gently rubbed and rolled on the nasopharynx and left in place for twenty seconds to absorb secretions. Also, specimens were taken from the posterior pharynx and tonsillar areas being careful to avoid touching the tongue, teeth, and gums.

The swab was gently brought out and inserted into the virus transport media (VTM), triple packaged and transported to the Genomics laboratory at Barau Dikko Teaching Hospital and Yusuf Dantsoho Memorial Hospital for molecular analysis for COVID-19 using real time PCR machine.

The SARS-CoV-2 RNA was extracted using QIAamp® Viral RNA Mini Kit (Qiagen, Germany) following manufacturer's instructions. The SARS-CoV-2 targets were detected using Detection Kit for 2019 Novel Coronavirus (2019-nCoV) (DaAn Gene primer kits; Sun Yat-sen University, Ghangzhou, China) following manufacturer's instructions. The BKC-PCR 16, (Jinan Biobase Biotech co. ltd, China) was used for the amplification and detection of the virus in the samples.

Statistical Analysis

All relevant data were entered and analyzed with IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) software version 23. Data were summarized using cross tab and frequency tables. Bivariate and multivariate logistic regression models were applied to check for statistically significant association between the dependent and independent variables. The p-value below 0.05 was considered as statistically significant.

RESULTS

The socio-demographics characteristics of the respondence are shown in Table I. About a third of respondents 223 (34.5%) were below 30 years, which is similar in those greater than 49 years (216, 35.6%). Four hundred and fifty-four were male, of which 95 (20.3%) were positive and 316 participants were female, of which 56 (17.7%) were positive for COVID-19. Participants' socio-demographics for Malaria infection is depicted in Table 2. The test positivity rate of COVID-19 was 19.6%, with 151 out of 770 participants testing positive for COVID-19

Table 1: Demographic characteristics of study participants

Characteristics	**COVID 19 Status**	
	Positive Frequency (%)	Negative Frequency (%)
Age		
Mean age	38.7 ± 14.8	39.63 ± 16.3
<30	45 (29.8)	178 (28.8)
30-49	68 (45.0)	263 (42.5)
>49	38 (25.2)	178 (28.8)
Total	151(100)	619(100)
Sex		
Male	95(62.9)	359 (58.0)
Female	56(37.1)	260 (42.0)
Total	151(100)	619(100)

There was no statistically significant association between COVID -19 status and the socio -demographic characteristics of the participants.

Prevalence of Malaria and Typhoid Fever

Prevalence of Malaria was 11.7 %, (n= 90/770) and Typhoid fever was 25.8% (n= 199/770). Typhoid fever was the most prevalent illness in the study group followed by COVID-19 (19.6%) and Malaria (11.7%). The co-infection rate of Malaria and Typhoid fever was 2.9%. Covid /Typhoid co-infection was most common in the study population (27.8%), followed by Covid/Malaria co-infection (13.9%) (Table 3)

Table 2. Association between sociodemographic characteristics and COVID-19, Malaria and Typhoid status

Variable	COVID-19 Status			MALARIA Status			TYPHOID Status		
	Positive Frequency (%)	Negative Frequency (%)	Test statistics	Positive Frequency (%)	Negative Frequency (%)	Test statistics	Positive Frequency (%)	Negative Frequency (%)	Test statistics
Age									
Mean age	38.7 ± 14.8	39.63 ± 16.3		38.7 ± 14.8	39.63 ± 16.3		38.7 ± 14.8	39.63 ± 16.3	
<30 years	45 (29.8)	178 (28.8)	$\chi2$ =0.787	36 (37.1)	187 (27.8)	$\chi2$=3.888	63 (31.8)	160 (28.0)	$\chi2$=5.314
30-49 years	68 (45.0)	263 (42.5)	P =0.675	36 (40.2)	292 (43.4)	P=0.143	92 (46.5)	239 (41.8)	P=0.070
>49 years	38 (25.2)	178 (28.8)		22 (22.7)	194 (28.8)		43 (21.7)	173 (30.2)	
Total	151(100)	619(100)		97(100)	673(100)		198(100)	572(100)	
Sex			$\chi2$=1.213			$\chi2$=1.000			
Male	95(62.9)	359 (58.0)	P =0.271	57(58.8)	397 (59.0)	P =0.966	106 (53.5)	348 (60.8)	$\chi2$=3.243
Female	56(37.1)	260 (42.0)		40(41.2)	276 (41.0)		92(46.5)	224 (39.2)	P=0.72
Total	151(100)	619(100)		97(100)	673(100)		198(100)	572 (100)	

There was no statistically significant association between COVID-19 status, Malaria status, typhoid status and the socio-demographic characteristics of the participants.

Table 3: COVID-19 infection with other febrile infections N=151

Febrile infections	**COVID status**	
	COVID-19 +ve **Frequency (%)**	**COVID-19 -ve** **Frequency (%)**
Malaria	21(13.9)	130(86.1)
Typhoid	42(27.8)	109(72.2)

Covid/Typhoid co-infection was most common (27.8%), followed by Covid/Malaria co-infection (13.9%)

There were significant association between symptoms of fever (p=0.001), cough, sore throat (p=0.001), loss of smell (p=0.001), chills (p=0.001) and chest pain (p=0.001) and COVID-19 positive participants. However, multivariate logistic regression showed that symptoms of fever (OR14. 224; 95% CI, 6.754-29.956), cough (OR 2.825; 95% CI 1.058-7.547), loss of taste (OR, 0.270; 95% CI, 0.111-0.654), loss of smell (OR 71.292; 95% CI, 33.140-153.368) and chills (OR, 3.455; 95% CI, 1.535-7.775) were significant predictors of COVID-19 infection as shown in Table 4.

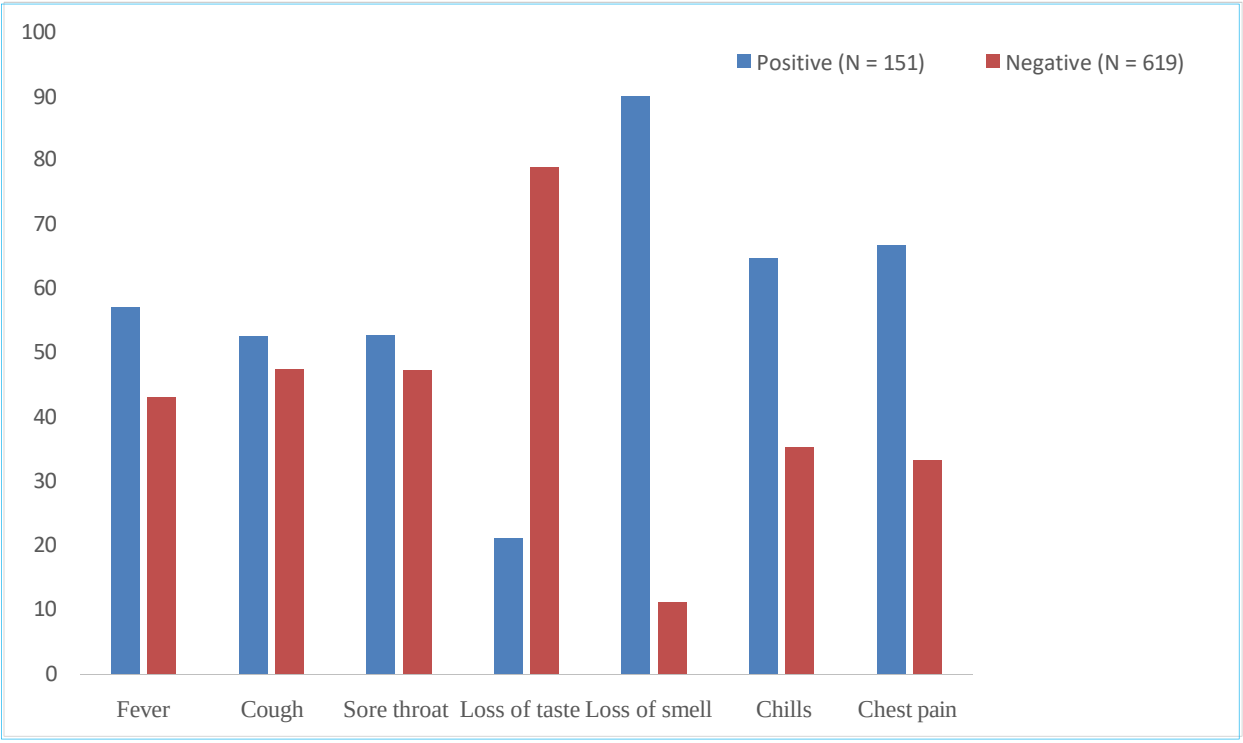

Fig 1. Symptom distribution of COVID-19 positive and COVID-19 negative participants

Table 4: Symptoms among participants by SARS-CoV-2 test results & multivariate logistic regression analysis of predictive symptoms for COVID 19 infection

		Participants by SARS-CoV-2			Multivariate logistic regression	
Symptoms	**Overall (N =770)**	**COVID-19 Status**		**P value**	**OR (95% CI)**	**P value**
		Positive	**Negative**			
Fever	214	122 (57.0)	92(43.0)	0.001*	14.224(6.754-29.956)	0.001*
Cough	78	41(52.6)	37(47.4)	0.001*	2.825(1.058-7.547)	0.038*
Sore throat	89	47 (52.8)	42(47.2)	0.001*	1.181 (0.481-2.899)	0.717
Loss of taste	90	19(21.1)	71(78.9)	0.718	0.270(0.111-0.654)	0.004*
Loss of smell	126	112 (89.8)	14(11.2)	0.001*	71.292(33.140-153.368)	0.001*
Chills	85	55(64.7)	30(35.3)	0.001*	3.455(1.535-7.775)	0.003*
Chest pain	33	22 (66.7)	11(33.3)	0.001*	2.889(0.762-10.949)	0.119

*Keys: OR: odds ratio, CI: confidence interval, *statistically significant at P<0.05*

DISCUSSION

The mean age of the participants who were COVID-19 positive was 38 years; with the majority of COVID-19 and malaria patients falling into 30 - 49-year age range. These findings were similar to the research findings from Lagos, Southwest, Nigeria.[12] Age showed no association with infection in this study. In this study, male participants accounted for a higher percentage of those who were COVID-19 positive. This figure is probably because males accounted for a higher number of participants. In terms of sex, the male sex has been said to be a major risk factor associated with the spread of contagion as well as the mortality rate in COVID-19 infection.[12] This was further corroborated by other authors who also reported higher percentage of COVID-19 in male patients.[13, 14, 15]

The test positivity rate of Covid-19 in this study was 19.6%. (Table 1) This is much higher than the 5.6%, revealed as that for the Country in a study conducted roughly about the same time [16]. This difference may be due to the varying responses to the general screening for Covid-19 by different states in the country, some more than others and in some states, screening was minimal.

Early diagnosis and treatment of malaria has been proven to reduce disease, deaths, and transmission. WHO recommends that all suspected cases of malaria be confirmed using parasite-based diagnostic testing (through either microscopy or a rapid diagnostic test). Diagnostic testing enables health providers to swiftly distinguish between malarial and non-malarial fevers, facilitating appropriate treatment.[17]

Typhoid fever had a 25.8% prevalence rate in this survey. In Nigeria, some data on typhoid fever prevalence has been documented by some researchers, ranging from 4% in Oyo state to 15% in the North western region .[20, 21]

Typhoid fever remains a major disease because increased urbanization, inadequate supplies of potable water, regional movement of large numbers of immigrant workers, inadequate facilities for processing human waste, overburdened health-care delivery systems, are some factors that contribute to the development and spread of *S. Typhi*.[21] However, the true incidence of typhoid fever is difficult to evaluate in Nigeria because of the lack of a proper coordinated epidemiological surveillance system

COVID-19 (primary infection) patients who become infected and test positive for other pathogens (secondary infections) are said to be co-infected. Co-infection and superinfection of pathogens in COVID-19 patients is a critical issue as it is difficult to distinguish the associated complications.[12] In this research, the findings revealed that typhoid was the most prevalent co-infection with COVID-19 in the study group followed by malaria. (Table 3)

Malaria/Typhoid fever coinfection was 2.9%. Generally, microbial co-infections are another primary concern in patients with COVID-19. Sahu reported that microbial co-infections are hospital-acquired/nosocomial infections, and patients admitted to intensive care units with invasive mechanical ventilation are highly susceptible to them[14]. The COVID-19 positive patient's immune systems may be already compromised and weakened, consequently making them susceptible to bacterial, fungal, or viral co-infections. The non-availability of specific guidelines or treatment options for these types of co-infections at the moment may contribute to morbidity and mortality among patients.

Typhoid fever (25.8%) was the most prevalent illness in the study group followed by COVID-19 (19.6%) and Malaria (11.7%) at the period the survey was carried out in the state. Co-infection of COVID-19 with different organisms has been reported in different part of the World too such as in places like Bahrain, Iran, United Arab Emirate and Saudi Arabia.[22,23,24,25,26,27] The most common bacterial species they reported were *Klebsiella pneumonia, Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, Staphylococcus aureus, Enterococcus faecalis,* and *Enterococcus faecium, Haemophilus influenzae, Streptococcus pneumoniae*. The co-infection often cuts across all age groups.[22, 23,24,25,26,27]

Co-infection with malaria in endemic regions was of high clinical importance as the pandemic spread.[28] Both malaria and COVID- 19 have similar signs and symptoms consisting of fever, myalgia, difficulty in breathing, fatigue and acute onset headache [28,29] and both have similar aspects and seem to have a strong potential for mutual influence.[28,29,30] The co-infection rate observed agreed with Onosakponome [31] in the findings from their research on the role of sex in malaria-COVID-19 co-infection and some associated factors in Rivers State, Nigeria. Also, multivariate logistic regression showed that the symptoms of fever, cough, loss of taste, loss of smell and chills were significant predictors of COVD-19 infection in this community.

There is urgent need for enhanced sensitization on the potential of COVID-19/malaria/Typhoid fever co-infections and further guidance to clinicians on the importance of testing for other causes of febrile illness more so in this period when there is much emphasis to early detect and isolate COVID-19 in a bid to contain further spread of the disease.

The limitations of our study are worthy of note. Typhoid serology may be associated with false positive tests which could potentially overestimate typhoid infection. Additionally, due to financial constraints, we were unable to include participants from all the LGAs of the state, hence, this may potentially impact the generalizability of our findings.

We recommend that health workers perform rapid tests for malaria and typhoid fever and for other causes of acute febrile illnesses, as they screen for COVID-19 infection. This presents an opportunity to respond to three infectious diseases at once and probably reduce unnecessary morbidity and deaths. By rapidly ruling out malaria and typhoid fever, the health workers can focus on the true cause of illness and administer appropriate management. Strengthening febrile diseases diagnosis and management long term, both locally and at a national level will go a long way to support elimination efforts and advance preparedness for future outbreaks.

DECLARATIONS

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Authors Contributions: "IO and BS designed the research study. BS, TZ and TI collected the research data. NG, OA and SJ analyzed the data. IO, KS, US and IS wrote the paper. Manuscript editing and review was done by IO and OT. All authors have read and approved the final manuscript".

Ethical Approval

Ethical approval for the study (MOH/AMD/744/VOL.1/921) was obtained from the State Ministry of Health's Research Ethics Committee. Informed oral and written consent were obtained from all participants after a detailed explanation on the nature of the study was given to them.

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