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Co-infection of COVID-19 and Malaria Exacerbates Fibrinolytic Responses: A Case-Control Study in Port Harcourt, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In late 2019, China experienced an outbreak of a new beta-coronavirus. COVID-19 had caused more than 3.7 million confirmed cases and killed at least 260,000 worldwide as recorded in April 2020. COVID-19 is mainly transmitted to susceptible humans through infected nasal droplets which are released via coughing, talking, or sneezing while malaria is a major public health issue in Africa

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especially in the sub-Saharan region. Malaria is mainly transmitted through the bites of infected female *Anopheles* mosquitoes. The hypercoagulable state thus reported in severe malaria infection has also been reported in COVID-19 infection but there is a paucity of information focusing on the trend and actual levels of these fibrinolytic biomarkers which can be established as a distinguishable level between the two coagulable conditions. Therefore, this study of some fibrinolytic markers (D-dimer and fibrinogen) in COVID-19 and malaria subjects in Port Harcourt will enlighten healthcare providers on associations between COVID-19 and malaria-infected patients. The cross-sectional, case-control study design was employed for this study. A total of fifty-five (55) malaria-positive subjects, fifty-five (55) COVID-19-positive subjects, fifty-five (55) co-infected subjects and fifty-five (55) control subjects who were within the ages of twenty (20) to sixty-five (65) years old participated in the study. Five milliliters (5ml) of venous blood was collected aseptically and dispensed into an Ethylene Diamine Tetraacetic acid (EDTA) anticoagulant bottle for malaria parasite detection from the thick blood film. A Sandwich-type Enzyme-Linked Immunosorbent Assay (ELISA) was used to assay for the D-dimer and fibrinogen levels while a nasopharyngeal swab was collected for confirmation of COVID-19-positive subjects using the RT-PCR technique. The mean values of D-dimer of the subjects were as follows; malaria parasite subjects (429.60 ±59.87 ng/ml), COVID-19 subjects (431.34 ±55.51 ng/ml), COVID-19 + malaria subjects (553.42 ± 59.74 ng/ml) and control subjects (319.86±51.93 ng/ml). These results revealed that the mean D-dimer values were statistically higher among the co-infected subjects (F-value= 2.816, p-value= 0.040), No significant changes were observed for fibrinogen among the studied subject groups (p=< 0.05). Sex exerted more significance on the studied parameters than age. Amongst the fibrinolytic parameters studied, D-dimer appears to possess potential diagnostic value for mild/asymptomatic COVID-19 infection and the case is not different in malaria infection in the tropical region of Nigeria. The D-Dimer levels were more significantly elevated in subjects with COVID-19 and malaria than in the other three groups. These results present evidence of the dual impact of COVID-19 and malaria infections in the tropics.

Keywords: COVID-19; fibrinolytic markers; co-infection; Malaria; Nigeria; Port Harcourt.

1. INTRODUCTION

"Coronavirus disease (COVID-19) is a mild to severe respiratory illness that is caused by a coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the genus Betacoronavirus, and is transmitted chiefly by contact with infectious material such as respiratory droplets, objects or surfaces contaminated by the causative virus, and is characterized especially by fever, cough, and shortness of breath and may progress to pneumonia and respiratory failure" [1]. "The virus is a member of the coronavirus family that are zoonotic pathogens, i.e., the viruses cause and transmit illnesses between humans and several animal species such as cattle, camels, cats, and bats" [2].

"The COVID-19 disease was detected initially in late December 2019 in Wuhan, Hubei Province, China, and spread worldwide two months later. About 200 countries over the entire world have reported different numbers of cases; however, the disease has drastically expanded in the United States, Spain, Italy, Germany, France, China, Iran, the United Kingdom, and Turkey" [3]. "COVID-19 had caused more than 3.7 million confirmed cases and killed at least 260,000 worldwide as recorded in April 2020" [4].

"Malaria remains a highly prevalent disease in more than 90 countries and accounts for at least 1 million deaths every year according to the World Health Organization malaria report of 2016. Malaria is a serious infectious disease caused by a peripheral blood parasite of the genus Plasmodium. Five species of parasites affect humans - *P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi.* Of these, *P. falciparum* is the most deadly form that can lead to cerebral malaria, and *P. vivax* has a wider distribution than *P. falciparum* because it can develop in the Anopheles mosquito vector at lower temperatures" [5].

"While malaria and COVID-19 can have similar presentation, common symptoms they share include but not are limited to: fever, breathing difficulties, tiredness, and acute onset of headache, which may lead to misdiagnosis of malaria for COVID-19 and vice versa, particularly when clinicians rely mainly on symptoms. Although respiratory signs and symptoms are

most pronounced in COVID-19 infection, a typical malarial disease complicated with Acute Respiratory Distress Syndrome (ARDS) is nearly not differentiable from severe COVID-19 infection" [6].

"COVID-19 coagulopathy linked to increased D-dimer levels has been associated with high mortality [7] and elevated D-dimer is accepted as a fibrinolytic biomarker in COVID-19 but in this study, we will look into fibrinogen and D-dimer as some fibrinolytic biomarkers which are mostly instrumental during fibrinolysis, comparing these variables in COVID-19 subjects with those suffering from malaria infection to see if there are any significant changes in these fibrinolytic biomarkers".

This study assessed the impact of COVID-19 and malaria on some fibrinolytic markers among subjects infected with COVID-19 and malaria infections in Port Harcourt.

2. MATERIALS AND METHODS

2.1 Experimental Design

A cross-sectional, case-control study design was employed to do a comparative study of some fibrinolytic markers in 55 COVID-19-confirmed subjects, 55 malaria-positive subjects, 55 COVID-19 and malaria co-infected subjects and 55 healthy subjects.

2.2 Study Area

The study was carried out at the Rivers State University Teaching Hospital Port Harcourt, Rivers State in the Port Harcourt City Local Government area of Rivers State, Nigeria. Port Harcourt covers a land area of $360 km^2$ and a population of 1,382,592 at the 2006 census. "Port Harcourt is the capital and largest city in Rivers State, Nigeria. It is the fifth most populous city in Nigeria after Lagos, Kano, Ibadan, and Kaduna. It lies along the Bonny River and is located in the Niger Delta. As of 2016, the Port Harcourt urban area had an estimated population of 1,865,000 inhabitants, up from 1,382,592 in 2006" [8]. "The population of the metropolitan area of Port Harcourt is almost twice its urban area population with a 2021 United Nations estimate of 3,171,076" [9]. "Port Harcourt has grown by 150,844 since 2015, which represents a 4.99% annual change" [10].

2.3 Study Population

The study was carried out among male and female subjects infected with malaria, COVID-19 and Co-morbidities of the two diseases against control of apparently healthy individuals. A total of fifty-five (55) malaria-positive subjects, fifty-five (55) COVID-19-positive subjects, fifty-five (55) co-infected subjects and fifty-five (55) control subjected were recruited for this study between the ages of twenty (20) to sixty-five (65) years old.

2.4 Sample Size

The sample size was determined using Cochran's Formula (Kotrlik et al. 2021)

$$n = \frac{z^2(pq)}{e^2}$$

Where n = sample size
z = Z-score (1.96)
p = Prevalence (taken from previous studies)
q = 1-p
e = margin of error (0.05)

The sample size for this study was fifty-five (55) subjects, as calculated based on the prevalence of COVID-19 in Rivers State which was reported as 6% [11].

Inclusion Criteria:

The participants in this study fulfilled the following inclusion criteria;

1. Subjects between the age range of 20 -65 years.
2. Apparently healthy subjects as the control.
3. Confirmed COVID-19 subjects.
4. Confirmed malaria subjects.
5. Confirmed co-infected subjects with COVID-19 and malaria.
6. People Resident in Port Harcourt.

Exclusion Criteria:

The exclusion criteria include:

1. Subjects below the age of 20 or above 65.
2. Subjects who refused to give consent.
3. Persons suffering from known thrombotic disorders that are not COVID-19 or malaria-related.
4. Persons on any form of anticoagulant therapy.
5. Subjects vaccinated against COVID-19.
6. People resident outside Port Harcourt.

2.5 Sample Collection and Processing

Five milliliters (5 ml) of venous blood was collected aseptically and a half (2.5 ml) was

dispensed for test and control participants in an Ethylene Diamine Tetraacetic acid (EDTA) anticoagulant bottle for malaria parasite detection from the thick blood film and 2.5 ml of blood was dispensed into to 0.3 ml of Trisodium Citrated anticoagulant bottle that was used for estimation of the fibrinolytic markers. Then nasopharyngeal swab was collected for confirmation of COVID-19-positive subjects by RT-PCR.

2.6 Laboratory Analysis

The D-Dimer and fibrinogen levels were determined using Sandwich Enzyme-Linked Immunosorbent Assay (ELISA); malaria infection was determined using microscopy, while COVID-19 status was determined using the RT-PCR technique.

2.6.1 Procedure for d-dimer and fibrinogen level determination using sandwich enzyme-linked immunosorbent assay (ELISA) technique as described by Gan et al. (2013)

Aliquotes of 100 µl of standard, blank and sample were added to the appropriate wells and incubated for 90 minutes at 37°C, and then the liquid was decanted from the wells and 100 µl of Biotinylated Detection Ab/Ag was added to each well, and incubated for 1 hour at 37°C then the solution from each well was decanted and 350 µl of wash buffer was used to wash wells 3 times after aspirating and then 100 µL of HRP conjugate was added and allowed to incubate at 37°C for 30 minutes then the solution in the wells was decanted and washed with the wash buffer 5 times after which 90 µL of the substrate reagent was added to the wells and allowed to incubate for 15 minutes at 37°C then 50µl of stop solution was added then the determination of the optical density (OD) of each well at once was done with a micro-plate reader set to 450nm.

2.6.2 Calculation of results

The average of the duplicate reading for each standard and sample was done then the average zero standard optical density was subtracted, and then a four-parameter logistic curve was plotted on a log-log graph paper, with standard concentration on the x-axis and OD values on the y-axis. When the OD value of the sample is out of the upper limit of the standard curve in the sandwich, a re-test was done with an appropriate dilution, then the actual concentration was obtained by multiplying the calculated concentration by the dilution factor.

2.6.3 Procedure for Thick blood film malaria parasite detection using microscopy as described by Hathiwala et al. [12]

The thick well-labeled blood film was prepared on a clean grease free glass slide. Whole blood from the EDTA bottle was collected within one hour of the collection, a well-labeled grease-free glass slide was used to make a thick film about 1.5 to 2 cm area in diameter from the EDTA collected blood sample then the slide was allowed to air dry then the dried thick smear on the slide was dehemoglobinized by dipping the dried slide into a beaker containing normal water and was removed immediately and allowed to air dry then it was stained using Giemsa stain with a buffer of pH 7.2. Fresh working Giemsa stain was prepared by adding 1 ml Giemsa stain stock to 39 ml of working Giemsa buffer; two drops of 5% Triton X-100 were added to the mixture later. The mixture was then poured into a standing 40-ml Coplin jar until full. Thick malaria smears were placed in the Giemsa stain (2.5%) for 45–60 minutes. At the end of the staining period, slides were removed and rinsed by dipping 3–4 times in the Giemsa buffer. The slides were left in the buffer for 5 minutes after which it was dry upright in a rack. A positive smear was included with each new batch of working Giemsa stain for quality control. Examination of the slide was made microscopically first by focusing using the 10-X objective before the 100-X oil immersion was used by the application of the immersion oil to the middle of the slide and lowering the objective to touch the oil then the examination of the slide was carried out and a minimum of 200 fields was examined.

2.6.4 Procedure for COVID-19 confirmation by RT-PCR molecular method as described by Arya et al. [13]

The volumes of Super Mix and Enzyme Mix per reaction multiply with the number of samples, which includes the number of controls and samples prepared. Molecular Grade Water was used as the negative control. For reasons of imprecise pipetting, an extra virtual sample was added then the sample was mixed completely and then spun down briefly with a centrifuge; then 20µL master mix with micropipettes of sterile filter tips was pipetted to each of the Real-Time PCR reaction plate/tubes then 5µL template (nucleic acid extracted from negative control and specimen, positive control without extraction) was separately added to different reaction plates/tubes; then the plates/tubes were

immediately close to avoid contamination; then to collect Master Mix and template in the bottom of the reaction tubes it was Spun down briefly then the instrument of ABI Prism®7500/7900 was used to Perform protocols as instructed by the manufacturer, it was ensured that for the ABI Prism® system "none" was selected as passive reference and quencher to avoid any errors.

2.7 Data Analysis

Data management and statistical analyses were conducted using SAS 9.4 software and graphical representations were carried out using the JMP statistical discovery™ software version 14.3. The fibrinolytic markers of the subjects were initially subjected to descriptive statistics that includes means, standard deviation, and 95% confidence intervals. Subsequently, analysis of Variance (ANOVA) was done to determine, if differences exist across the measured parameters by the subject group (Non COVID-19 or Malaria (Control), Malaria Positive, COVID-19 Positive, and COVID-19 + Malaria Positive. In addition, interaction effects between the subject groups by sex were also evaluated where p-values less than 0.05 were considered statistically significant.

3. RESULTS

Table 1. Demographic characteristics of participants in the study

Parameters	Study groups (n=55)	Control group (n=55)
Number of females	22	22
Number of males	33	33
Age range (years)	20-65	20-65

Table 2. some fibrinolytic markers of study subjects infected with COVID-19 and malaria

Treatment/Subject	N	Fibrinogen (ng/ml)	D-dimer (ng/ml)
Non COVID-19 or Malaria (Control)	55	55.36±2.03	319.86±51.93[a]
Malaria Positive	55	54.11±1.56	429.60 ±59.87[a]
COVID-19 Positive	55	57.48±2.57	431.34 ±55.51[a]
COVID-19+ Malaria Positive	55	58.32±2.79	553.42 ± 59.74[b]
F-value		0.7116	2.816
P-value		0.5461	0.040
Remark		NS	S

All levels were compared using Tukey-Kramer HSD
Within parameters, means with different superscripts are significantly different at p<0.05

Table 3. Values of some fibrinolytic markers of study subjects infected with COVID-19 and malaria by sex

Subjects	Sex	Mean ±SD	t-value	p-value	Remarks
Fibrinogen (ng/ml)					
Malaria Positive	Female (n=22)	51.79±2.07	1.254	0.216	NS
	Male (n=33)	55.53±2.15			
COVID-19 Positive	Female (n=22)	51.47 ±2.48	2.160	0.036	S
	Male (n=33)	61.16 ± 3.73			
Co-infection	Female (n=22)	60.76±3.53	1.398	0.169	NS
	Male (n=33)	61.12±3.90			
D-dimer (ng/ml)					
Malaria Positive	Female (n=22)	373.48±69.34	1.144	0.021	S
	Male (n=33)	521.16±108.89			
COVID-19 Positive	Female (n=22)	381.74±96.77	34.947	0.013	S
	Male (n=33)	461.74±67.78			
Co-infection	Female (n=22)	518.71±74.93	0.731	0.044	S
	Male (n=33)	530.05±98.03			

All levels were compared using Tukey-Kramer HSD
Within parameters, means with different superscripts are significantly different at p<0.05

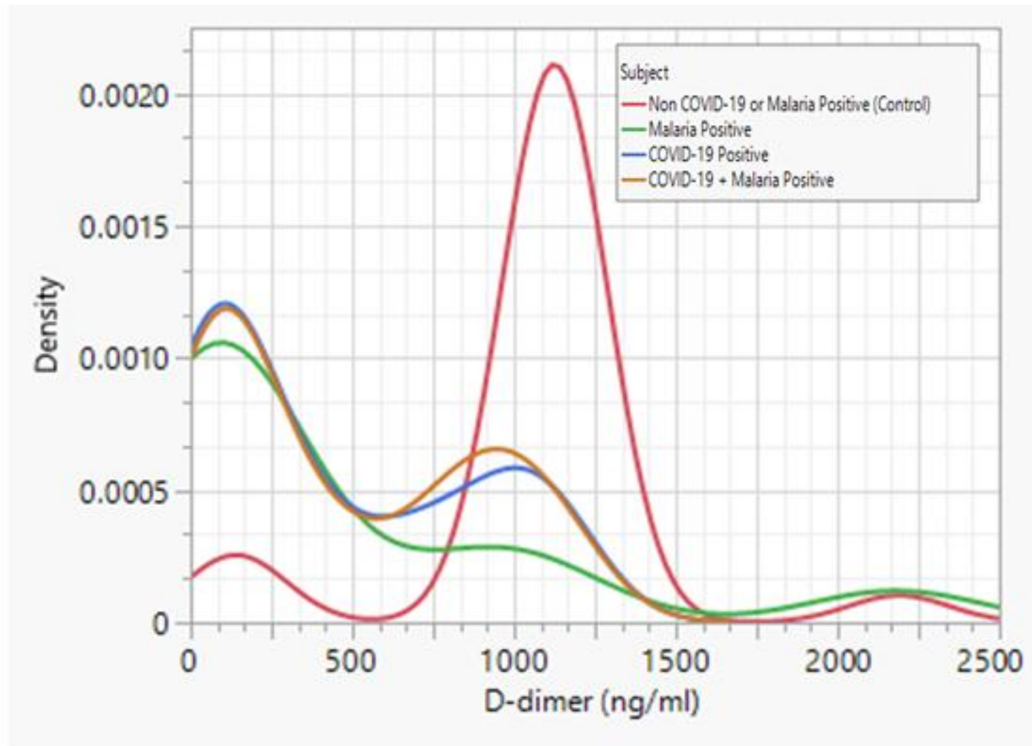

Fig. 1. Comparison of densities of d-dimer in COVID-19 and malaria-positive subjects

4. DISCUSSION

"The fibrinolytic markers considered in this study are D-Dimer and fibrinogen. Previous studies haves shown that the elevation of D-dimer indicates a hypercoagulable state in a patient with COVID-19 and reflects activation of coagulation and fibrinolysis" [14]. "D-dimer is often elevated during malarial infections" [15]. "*P. falciparum* is well known to cause adherence of infected red blood cells to the endothelium, causing damage, activation of the coagulation cascade, and, subsequently, elevating D-dimer levels" [15].

In this study, a statistically significant increase in the D-dimer levels of the co-infected subjects was observed when compared to the non-COVID-19 or malaria control. It is well known that COVID-19 and malaria produce a procoagulant state by inducing tissue factor expression, causing endothelial dysfunction and activating the coagulation cascade. "The hypercoagulable state of COVID-19 is associated with a high rate of venous and arterial thrombotic complications. However, malaria is usually associated with micro-thrombotic complications, but thrombosis of larger vessels, including cerebral venous thrombosis and pulmonary embolism, has been reported" [16].

This agreed with a study conducted by Meltzer [15] which stated that "D-dimer levels were considerably greater in *P. falciparum* malaria cases compared to non-falciparum malaria cases". The findings of the study also agree with the study conducted by Lehmann, [17] which observed "D-dimer elevation in patients with acute COVID-19 due to acute lung injury itself or due to thromboembolic complications that occur frequently in COVID-19". The above was seen from this study, that a significantly higher D-dimer level for the co-infected subjects was observed when compared to malaria-positive and COVID-19-positive subjects alone or when compared to the non-COVID-19 or malaria-control subjects.

When the mean value of D-dimer for subjects infected with COVID-19 and malaria by sex was compared, it was observed that among the studied groups, all the positive subjects and co-infected subjects had a statistically significant increase in the mean values, and among the male and female participants. The male subjects had higher significant levels than the female

participants as a result of the high expression of coronavirus receptors (ACE 2) in males [18].

In this study from the overall pool there was no statistically significant difference in fibrinogen levels when compared to the control subjects but amongst the four (4) subject groups studied, COVID-19 and malaria co-infected subjects had a higher mean value when compared to the control and the other subjects groups. But when comparing the mean values of fibrinogen of subjects infected with COVID-19 and malaria by sex. Among the studied groups, a statistically significant increase was found to exist among the COVID-19-positive subjects, with a higher mean value observed in the male participants. “From a study the biological differences in the immune systems between males and females exist which may impact the ability of females to fight infection including SARS-2-CoV-2 better than the males. Generally, females are more resistant to infections than males, and this is possibly mediated by the high expression of coronavirus receptors (ACE 2) in males” [18]. According to Arachchillage and Laffan, [19], “patients with severe COVID-19 are susceptible to coagulation as a result of increased levels of coagulation factors and fibrinogen is one of them”. This agrees with a study by Godoy et al. [20] that increased D-dimer and fibrinogen levels together with prolongation of the activated partial thromboplastin time (aPTT) promote coagulopathy in COVID-19 patients.

From the density plot of D-Dimer, when observing the density plot for the control subject there was no skewness in its distribution while for the other studied groups there was a right skew and the peak was found among the malaria-positive and COVID-19-positive subjects this indicated that subjects had clotting issues that lead to fibrinolytic activity, which D-dimer as a fibrin degradation product was raised. This agrees with Di Gennaro et al. [21] that among malaria and COVID-19 patients, there have been reports of high D-dimer levels in severe cases of COVID-19 and malaria infection.

From the density plot, it was observed that sex exerted a significant influence on the parameters which agrees with the study by Onosakponome and Wogu, [22] on the role of sex in Malaria-COVID19 co-infection and some associated factors in Rivers State, Nigeria. Where it was observed that there was a significant association between the co-infection with sex, and males had a higher value than females.

5. CONCLUSION

From this comparative study of some fibrinolytic markers of subjects infected with malaria and COVID-19, D-dimer was significantly raised among the co-infected subjects. D-dimer possesses a potential diagnostic value for mild COVID-19 and malaria infection.

6. RECOMMENDATION

D-Dimer should be incorporated as a surrogate diagnostic tool in mild asymptomatic COVID-19 and malaria-infected patients.

CONSENT

Written informed consent was obtained from participants before blood collection. Participants were made to understand the nature of the study and the fact that the participation is voluntary with confidentiality of recovered data maintained at all times during and after the study.

ETHICAL APPROVAL

For this study ethical approval was obtained from Rivers State Hospital Management Board.

CONTRIBUTION TO KNOWLEDGE

The comparative study revealed that D-dimer had more impact on the combined presence of COVID-19 and malaria co-infection than in COVID-19 and malaria-infected subjects alone and this impact was more on males than females.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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