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Research Article

Investigation of the Effect of Protein Nutritional Status, Previous Malaria Exposure, and Comorbidity on Biochemical and Haematological Indices of *Plasmodium falciparum* Malaria in Nigerian Children Under the Age of 5 Years

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Abstract

Background: Malaria threatened almost half of the world's population. A quarter of global malaria cases and deaths occur in Nigeria, mostly in children under the age of 5 years.

Objective: This study was aimed at determination of effects of protein nutritional status, prior malaria exposure, associated morbidity, and chloroquine treatment on biochemical and haematological parameters in children under 5 years with *Plasmodium falciparum* malaria.

Method: The nutritional status of the recruited children was assessed using the Advanced Paediatric Life support (APLS) formula, while malaria diagnosis, determination of bacterial and viral infection, and assessment of *Plasmodium falciparum* parasitaemia were carried out using standard microscopy techniques. The complete blood count was carried out using Beckman Coulter Analyzer.

Results: At mean age of 18.54 ± 1.59 months, the 93 children recruited for this study were not malnourished. The expected weight-for-age was 83.53% and 82.92% for the two groups. The expected height-for-age was 85.62% and 91.62% for the two groups. 44.08% of these children have previous history of malaria and 23.66% of the children were never infected with malaria. The malaria history of 32.26% of the children could not be ascertained. 54.35% of the 46 malaria subjects had bacterial infection, 6.52% had viral infection, and 39.13% presented only malarial parasite. There was no significant difference ($p < 0.05$) in all the parameters when compared based on malaria history and comorbidity.

Conclusion: The studied children were not malnourished. *P. falciparum* infection comorbidity is prevalent. Previous malaria exposure and comorbidities did not influence any of the parameters determined.

Keywords: Malaria; *Chloroquine*; Malnutrition; Comorbidity; Parasitaemia; Children

Introduction

Malaria due to *Plasmodium falciparum* is a leading cause of hospitalizations and deaths of children under 5 years in Africa [1,2]. According to World Health Organization (WHO), it is estimated that Nigeria accounted for about a quarter of the global malaria cases and deaths yearly between 2018 and 2020 [3-5]. Prevalence

of *P. falciparum* malaria around Jos metropolis of Plateau State, Nigeria has been well documented [6-8]. Despite the existence of effective treatment and protective measures, malaria continues to constitute a major public health concern, with high mortality in severe malaria cases [9]. There is a need to investigate factors that could contribute to the poor outcome in the intervention and management of malaria in this group of children. This study was designed to investigate the role of common comorbidities of *P. falciparum* malaria such as malnutrition, infection, as well as, the role of previous exposure to malaria on the pathogenesis of the disease. Comorbidities have been reported to compound the economic burden of malaria in Nigeria, and interventions to control malaria should also include control of the common comorbidities [10]. Sepsis has been reported to be the commonest comorbidity (40%) among children below 5 years with severe malaria, living in Port Harcourt, Nigeria [11]. Malnutrition is prevalent among many African children and it's a major cause of morbidity and mortality in these children. As in malaria, the most vulnerable group to malnutrition are the children under 5 years. Malnutrition comorbidity in *P. falciparum* is a significant risk factor. According to Kinyoki [12], malnutrition comorbidity with *Plasmodium falciparum* malaria has been associated with poor clinical outcome in children under 5 years. Therefore, there is need to integrate malnutrition intervention into malaria intervention program. Children under 5 years are said to be the most vulnerable to *P. falciparum* malaria because at that age the anti-body response to malaria is either not yet developed or inadequate to protect against severe infection. A study by Nhabomba [13], on children in Mozambique shows that the age at which a child had first exposure to malaria does not determine the acquisition of protective immunity by the child, but rather the antibody responses, are to a large extent influenced by both previous exposure and age. Also, Singer [14], reported that, in the regions of high malaria transmission, children of 3-18 months are at highest risk of malaria morbidity and mortality. And that the development of an anti-body response to malaria parasite does not depends on the frequency of previous malaria exposure in early stage. But in another study by Barau [15], children having previous malaria history had higher levels of antibodies response to malaria antigen when compared to children without malaria history. Chloroquine tablet is a non-prescription drug in Nigeria. It is affordable, readily available, and could be bought over the counter at any patent medicines stores across the country.

Re-emergence of sensitivity of malaria parasite to chloroquine in some areas where resistance was once prevalent has been reported by several recent studies [16]. And despite the ban on chloroquine in the treatment of malaria in Nigeria [17], it was reported that about 70% of mothers in Nigeria, still use oral chloroquine as the first-line treatment of suspect malaria symptoms in their children under 5 years [18]. In this study, we investigated how nutritional status, comorbidity, and previous exposure to malaria influence the impact of chloroquine treatment on the studied biochemical and haematological parameter.

Materials and Methods

Study design

Home-based administration of chloroquine tablets to children with suspected malaria is a common practice in the study area and Nigeria in general. This research work was designed to investigate the effects of nutritional status, prior malaria exposure, and comorbidity on parasiteamia, biochemical and haematological indices of *Plasmodium falciparum* infection in children between the age of 1 months and 59 months. To achieve the objectives, we determined the changes in the levels of parasitaemia, the biochemical and the heamatological parameters in the blood of non-treated *P. falciparum* infected children and their chloroquine treated counterparts, based on the presence of co-morbidity and previous exposure to malaria infection.

The chloroquine treatment, dosage, and administration

The home-based chloroquine-treated malaria subjects were children that were screened to have *P. falciparum* in their peripheral blood and were administered chloroquine tablets orally at home by their mothers, following observation of suspected malaria symptoms. The administration of chloroquine treatment was within 24 hours prior to hospital admission and blood sample collection. These chloroquine-treated children had no symptoms of any other disease and did not have a history of any other medication in that particular episode of the sickness. The working interval of 24 hours between oral chloroquine administration and sample collection was adopted from the average time interval recorded in the study area for the transfer of the children with malaria from home to the hospital in situations where immediate access to medical facility or medical attention is not possible.

An average dosage of 1 chloroquine tablet, containing 250 mg of Chloroquine phosphate, United States Pharmacopeia (equivalent to 150 mg base), administered orally in 24 hours was recorded from the mothers of these chloroquine-treated children.

The 16 chloroquine-treated children recruited for this study satisfied the inclusion criteria for simple and uncomplicated malaria. All the children that presented severe malaria on hospital admission did not receive any medication prior to blood sample collection.

Study area and location

Jos North, a local Government area of Plateau state, mainly Jos metropolis is the study site. Its geographical coordinates are 9° 55' 42" N (latitude) and 8° 54' 31" E (longitude).

Study subjects

The malaria-positive children attending the Emergency Pediatrics Unit (EPU), Pediatrics Department, Jos University Teaching Hospital (JUTH), Jos and Our Lady of Apostle (OLA) hospital, Jos were recruited as study subjects. While the malaria-negative healthy children attending the Child Welfare Center of the Department of Community Health and Pediatrics Outpatient Department (POPD) for immunization at JUTH were recruited as control for this study. The malaria positive children were recruited consecutively and divided into groups.

The Sample size for this study was determined using Krejcie and Morgan [19] table for determining sample size of finite population.

Inclusion criteria

The recruited children presenting uncomplicated malaria had fever and presence of *P. falciparum* in their blood sample, but without symptoms of any other sickness, and had no history of any medication before sample collection. While the children recruited for severe malaria had fever, presence of *P. falciparum* in peripheral blood, lumber puncture – sterile, and with at least one of the following conditions: unconsciousness or coma, altered sensorium, repeated convulsion in a 24-hour period. There were no symptoms of any other diseases, having no history of any medication in the particular episode of the sickness. The chloroquine-treated children were malaria positive, but were previously administered with oral chloroquine within 24 hours prior to sample collection. The control children were healthy and tested negative for malaria parasite screening, and they were within the same age bracket, living in the same area, and were not under any medication.

Clinical examination of subjects by clinician and data collection

All the children recruited for this study, were each examined by a clinician for anthropometric, demographic, and other diagnostic indicators of malaria. The record of malaria history was obtained from the mother. The child's age, sex, weight, height, and temperature were recorded. The weight was measured using a bathroom scale and the height was measured using height or length board depending on whether the child would stand unaided or not.

Assessment of the nutritional status of the recruited children was carried out using the Weech's formula, as adapted in advanced paediatric life support (APLS) formula [20-22] and applied at the Emergency Paediatrics Unit (EPU), Paediatrics Department, Jos University Teaching Hospital (JUTH), Jos.

Equipment and reagents

Standard laboratory equipment at Department of Biochemistry Laboratory, Faculty of Medical Sciences, University of Jos, and Department of Haematology laboratory, Jos University Teaching Hospital, were used for this research work. All reagents used were of analytical grade.

Sample collection and preparation

The collection of blood samples was carried out with the assistance of medical personnel. Five ml of venous blood was collected from each child by venipuncture, using a 5 ml syringe and needle. The 2 ml of collected blood was immediately dispensed into a Z5 tube containing an anticoagulant, Ethylene Diamine Tetra Acetic Acid (EDTA) solution. The tube was gently shaken and kept at room temperature pending the haematological analysis, which was carried out within 6 hours of sample collection.

The remaining 3 ml of the collected blood sample was allowed to clot in a sterile 10 ml tube, and centrifuged at 3000 rpm for 10 min. Then serum separated as supernatant was stored in a refrigerator until it was needed.

Malaria diagnosis and determination of bacterial and viral infection

The standard diagnosis of malaria by microscopic determination of malaria parasite in the thick and thin blood film on a slide using Leishman's stain and determination of bacterial and viral infection were carried out as described by Dace and Lewis [23], in all the recruited children. Malaria diagnosis was based on the presence of asexual stages of *P. falciparum* on the blood films. Determination of viral infection was based on the presence of reactive (atypical) lymphocytes in the blood, whereas bacterial infection was determined based on the presence of toxic granulation. The determination of complete blood counts was done using Beckman Coulter Analyzer according to Student health center manuals [24].

Data analysis

The analysis of the data obtained from this study was carried out using Statistical Package for Social Sciences (SPSS) version 21. One-way analysis of variance (ANOVA) was used to confirm the difference in means of several groups. An assessment of the normality of data was carried out using graphical method. The result of test of normality shows that the data obtained in this study were normally distributed. P- values less or equal to 0.05 ($p \leq 0.05$) were considered significant.

Results

Table 1 shows a total of 93 children aged 1-59 months were recruited consecutively for this cross-sectional study involving 46 malaria-positive children and 46 non-malaria healthy children living in Jos metropolis of Plateau state, Nigeria. Twenty three of the 46 malaria positive children (50%) were untreated and presented simple malaria, while 7 of them (15.22%) were untreated and presented severe malaria, and 16 of the children (34.78 %) were treated with chloroquine at home. The total number of male and female children within control group were 23 (49.84%) and 24 (51.06%), respectively. While the total number of male and female children within total malaria group were 24 (52.17%) and 22 (47.83%). Respectively.

The expected age-for-weight (malnutrition index) was 83.53% of the expected weight for the control children and 82.92% for the malaria children (Table 2). The expected age-for-height (stunted growth index) was 85.62% for the control children and 91.62% for the malaria children (Table 3). There was no significant difference ($p<0.05$) between values obtained for both the control and malarial groups in terms of the two indices of malnutrition. These anthropometric indices of protein-energy malnutrition indicate that all the children recruited for this study were not malnourished.

The history of prior malaria infection in all the 93 recruited children is summarized in Table 4. At a mean age of 18.54 ± 1.59 months, 44.08% of these children had previous history of malaria prior to the present episode, whereas 23.66% of the children were never infected with malaria. The malaria history in the remaining 32.26% of the children could not be ascertained. This result suggests that for children within this age bracket, exposure to malaria infection does not confer immunity against malaria parasite.

Table 5 shows the records of co-morbidity in malaria-positive children with concurrent bacterial or viral infections. In addition to malaria parasite, the majority of the children with malaria have either bacterial or viral infection. 25 of 46 malaria subjects had bacterial infection as evidenced from sepsis, whereas three or 6.52% had viral infection (atypical lymphocytes); and only 18 malaria subjects or 39.13% presented only malaria parasite and had neither bacterial nor viral infection. This implies that most malaria children recruited for this study have associated bacterial or viral infection.

Treatment Group	Age (months)	Weight(kg)	Height 9cm)	Temperature (°C)
Control Children	12.47 ± 1.60 (47)	8.42 ± 0.40 (47)	71.27 ± 1.32 (47)	36.80 ± 0.07 (47)
Non-treated Simple	27.22 ± 4.18[a]*	9.97 ± 0.97	83.69 ± 3.99[a]*	38.45 ± 0.25[a]*
Malaria Children	(23)	(23)	(23)	(23)
Non-treated Severe	19.00 ± 1.48	8.88 ± 0.44	75.71 ± 5.20	39.24 ± 0.47[ab]*
Malaria Children	(7)	(7)	(7)	(7)

Chloroquine	23.69 ± 3.67[a]*	10.68 ± 0.80[a]*	81.96 ± 3.25[a]*	37.94 ± 0.30[a]*
Treated Children	(16)	(16)	(16)	(16)
Total Malaria Children	24.74 ± 2.46[a]** (46)	10.05 ± 0.57[a]* (46)	81.88 ± 2.41[a]** (46)	38.40 ± 0.14[a]* (46)

Table 1: Anthropometric measurements and temperature of recruited children below 5 years in Jos metropolis.

Tabulated values are means ± S.E.M for (n) subjects given in parenthesis.

*The mean difference is significant at the $p < 0.05$ level, and **at $p < 0.01$ level

[a]- Comparing respective malaria infected group with control

[b]- Comparing untreated severe malaria group with chloroquine treated malaria group.

Treatment group	Average Age (months)	Expected weight (kg)	Mean actual weight (kg)	Number of Subjects (n)	Percentage of expected (%)	Inference
Control Children	12.47	10.08	8.42	47	83.53	Normal (not malnourished)
Malaria Children	24.74	12.12	10.05	46	82.92	Normal (not malnourished)

Table 2: Malnutrition Index: expected weight for age of the under 5 years subjects attending JUTH and OLA hospital in the Jos Metropolis.

Tabulated values are means ± S.E.M for (n) subjects given in parenthesis.

Treatment group	Mean Age (months)	Expected height (cm)	Mean actual height (cm)	№ of Subjects (n)	Percentage of expected (%)	Inference
Control-Children	12.47	83.24	71.27	47	85.62	Normal (not malnourished)
Malaria-Children	24.74	89.37	81.88	46	91.62	Normal (not malnourished)

Table 3: Stunted growth index: expected height for age in the under 5 years subjects attending JUTH and OLA hospital in Jos metropolis.

Tabulated values are means ± S.E.M for (n) subjects given in parenthesis.

Malaria history	Number of subjects	Percentage (%)
Positive -history	41	44.08
Negative-history	22	23.66
History unavailable	30	32.26
Total	93	

Table 4: Record of Previous Malaria History in Children under the age of 5 years.

Comorbidity	№ of subjects	Percentage (%)
Bacterial infection	25	54.35
P. falciparum only	18	39.13
Viral infection	3	6.52
Total	46	

Table 5: Results of malaria presenting with concurrent bacterial and viral infections in the under 5 years subjects.

*All subjects presented with *P. falciparum* malaria parasite infection.

As shown in table 6, in all cases, there was no significant difference between chloroquine treated children with previous malaria history and chloroquine treated children with no previous malaria history in respect of level of *parasitaemia,* temperature and duration of fever. Similarly for the three parameters, there was no difference between untreated malaria children with no previous malaria history and those with previous history of malaria. Table 7 shows that there were no differences in the values obtained for parasitaemia, temperature and duration of fever in treated and non-treated children with co-morbidity, and those with strictly malaria parasite alone.

As shown in table 8, for all comparisons, there were no significant differences between chloroquine treated children with previous malaria history, and chloroquine treated children with no previous malaria history in respect of values for; serum creatinine, serum albumin, serum total protein, serum globulin, serum aspartate aminotransferase, serum alanine aminotransferase and serum alkaline phosphatase. Likewise, there were no significant differences in the values of all determined biochemical parameters obtained for untreated children with no previous malaria history and those with previous history of malaria. This shows that previous exposure to malaria parasite does not affect the values of these biochemical parameters in the malaria children recruited for this study.

Table 9 indicates that, there were no significant differences between chloroquine treated children with co-morbidity and those without concurrent bacterial/viral infection in the respective biochemical parameters analyzed. There were no Significant differences in the results obtained for the biochemical parameters in the untreated children with associated viral or bacterial infection and those with only *P. falciparum* infection. This result demonstrates that the concurrent bacterial/viral infection does not have significant effect on the values obtained for the biochemical parameters analyzed as compared to children with strictly defined malaria.

Treatment Group	Parasitaemia (%)	Temperature ()	Duration fever (Days)
Positive-history treated Children	17.67 ± 0.71 (09)	38.04 ± 0.41 (09)	6.00 ± 1.67 (09)
Negative-history treated Children	19.00 ± 0.63 (05)	37.64 ± 0.58 (05)	7.60 ± 3.63 (05)
Positive-history untreated Children	35.39 ± 3.86 (18)	38.31 ± 0.27 (18)	4.94 ± 1.24 (18)
Negative-history untreated Children	39.43 ± 3.79 (7)	39.11 ± 0.47 (7)	3.00 ± 0.85 (7)
Tabulated values are means ± S.E.M for n subjects given in parenthesis			

Table 6: Effect of previous malaria history on parasitaemia, temperature and duration of fever in untreated children, and chloroquine treated children under 5 years attending JUTH and OLA hospital in Jos metropolis.

Treatment	Parasitaemia (%)	Temperature (^{0}C)	Duration of fever (days)
Treated children with comorbidity	17.92 ± 0.56 (13)	37.9 ± 0.33 (13)	6.38 ± 1.73 (13)
Treated children without comorbidity	19.00 ± 1.00 (3)	38.1 ± 0.91 (3)	5.0 ± 2.1 (3)
Untreated children with comorbidity	37.33 ± 2.71 (15)	38.92 ± 0.31 (15)	3.87 ± 1.34 (15)
Untreated children without comorbidity	35.67 ± 4.36 (15)	38.38 ± 0.31 (15)	4.33 ± 0.89 (15)

Table 7: Effect of malaria with concurrent bacterial/viral Infection on parasitaemia, temperature and duration of fever in untreated malaria, and chloroquine treated malaria under 5 years children attending JUTH and OLA hospital in Jos metropolis.

Tabulated values are means ± S.E.M for n subjects given in parenthesis.

Treatment group	Serum creatinine (µmol/l)	Serum albumin (g/l)	Serum total protein (g/l)	Serum globulin (g/l)	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (IU/L)	Alkaline phosphatase (IU/L)
Positive-history treated children	67.38 ± 6.48 (8)	35.00 ± 1.68 (8)	64.75 ± 3.02 (8)	29.75 ± 2.31 (8)	9.75 ± 1.33 (8)	8.0 ± 1.36 (8)	217.5 ± 39.67 (8)
Negative-history treated children	72.00 ± 13.98 (4)	31.50 ± 6.13 (4)	64.75 ± 13.66 (4)	33.25 ± 7.6 (4)	10.0 ± 1.41 (4)	9.0 ± 0.91 (4)	155.8 ± 28.16 (4)
Positive-history untreated children	83.59 ± 11.57 (17)	37.18 ± 1.55 (17)	72.29 ± 3.27 (17)	36.29 ± 2.34 (17)	8.88 ± 0.67 (17)	8.59 ± 0.77 (17)	167.5 ± 13.84 (17)
Untr	75.0 ± 19.87 (14)	38.43 ± 1.09 (7)	69.29 ± 2.93 (7)	30.86 ± 2.63 (7)	8.29 ± 1.36 (7)	7.71 ± 1.04 (7)	144.7 ± 20.44 (7)

Table 8: Effect of previous malaria history on biochemical parameters in untreated malaria, and chloroquine treated malaria under 5 years children attending JUTH and OLA hospital in Jos metropolis.

Tabulated values are means ± S.E.M for n subjects given in parenthesis.

Treatment groups	Serum creatinine (µmol/L)	Serum albumin (g/l)	Serum total protein (g/l)	Serum globulin (g/l)	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (IU/L)	Alkaline phosphatase (IU/L)
Treated children with comorbidity	69.09 ± 7.30 (11)	33.18 ± 2.29 (11)	61.27 ± 4.22 (11)	28.09 ± 2.38 (11)	9.27 ± 1.21 (11)	7.55 ± 1.15 (11)	193.27 ± 31.10 (11)
Treated children without comorbidity	75.33 ± 19.20 (3)	37.33 ± 2.67 (3)	78.0 ± 4.73 (3)	40.67 ± 2.33 (3)	9.33 ± 1.76 (3)	8.33 ± 0.88 (3)	159.00 ± 39.55 (3)
Untreated children with comorbidity	89.73 ± 15.9 (15)	36.13 ± 1.32 (15)	66.0 ± 3.14 (15)	29.87 ± 2.17 (15)	8.73 ± 0.80 (15)	9.07 ± 0.85 (15)	177.0 ± 15.57 (15)
Untreated children without comorbidity	71.14 ± 7.41 (14)	38.71 ± 1.31 (14)	77.86 ± 1.66 (14)	40.57 ± 1.46 (14)	8.35 ± 0.73 (14)	7.5 ± 0.64 (14)	133.14 ± 10.16 (14)

Table 9: Effect of malaria with concurrent bacterial/viral infection on biochemical parameters in untreated malaria, and chloroquine treated malaria under 5 years children attending JUTH and OLA hospital in Jos metropolis

Tabulated values are means ± S.E.M for n subjects given in parenthesis.

Discussion

The data generated from this study revealed that at mean age of 18.541.59 months, 44.08% of the children included in this study had previous history of malaria, while 60.87% of the *P. falciparum* malaria positive children had comorbidity bacterial or viral infection. The prevalent form of malaria in children under 5 years in Jos Metropolis, is uncomplicated *P. falciparum* malaria with septicaemia comorbidity. Thirty-nine out of 46 malaria-positive children (84.78%) presented uncomplicated malaria, while the remaining 7 children (15.22%) presented severe malaria cases.

There was no significant difference in the duration of fever (days) before hospital admission for all the malaria-positive groups. This suggests that the duration of fever before hospital presentation in this study area do not play a significant role in the observed diseases status of *P. falciparum* malaria on admission.

The results of the age for weight (malnutrition index) and age for height (stunted growth index) showed that all the children recruited for this study were neither malnourished nor stunted. Therefore, the effect of protein energy malnutrition on the clinical manifestations and treatment outcome of *P. falciparum* malaria in this group of children can be ruled out. The data generated from this study further showed that majority of the children recruited have previous history of malaria. All comparisons of biochemical and haematological parameters analyzed were not significantly different for studied children with previous malaria history and those without previous malaria history. Although Olomu [6] have reported mild anaemia in children under 5 years with *P. falciparum* malaria in Jos metropolis, and a report by Afolabi [8], ruled out involvement of kidney and liver as well as impairment of the functions of these organs in the pathogenesis of malaria in under 5 years malaria-positive children in Jos metropolis. This observation is in agreement with the reports that children under the age of 5 years are yet to develop immunity against malaria despite successive exposure to malaria infection and as such constitute most vulnerable group and are at a high risk of developing severe *P. falciparum* malaria [25].

The high-level of comorbidity observed in these malaria-positive children suggest that inclusion of tests for septicaemia in this group of children could prevent wrong or incomplete diagnosis, and as well could prevent inadequate or inappropriate treatment. There were no significant differences in the values obtained for all the parameters analyzed in both the children with comorbidity and those with strictly *P. falciparum* infection. This finding is in agreement with report of study from Uganda that co-infection with malaria did not seem deleterious [26].

Conclusion

From the pattern of the results obtained in this study we could conclude, that *P. falciparum* infection with septicaemia comorbidity is prevalent among under 5 years children in Jos Metropolis of Plateau state, Nigeria. The children were not malnourished, and there was no influence of duration of fever on the disease status on admission.; Septicaemia comorbidities and previous exposure to malaria did not have any significant impact on the values of the biochemical and hematological indices of malaria respectively, in these children.

Study Limitation

Many of the children that were for this research work have symptoms of other diseases and. Or, histories of non- chloroquine medications before blood sample collection and as such were not eligible to participate in the study.

Consent For Publication

Not applicable.

Funding

Not applicable.

"The authors declare that no funds, grants, or other support were received during the preparation of this manuscript".

Ethics Approval

The research protocol for this study was approved by the Medical and Health Ethics Committee of Jos University Teaching Hospital, Jos.

Consent to Participate

Informed consent and assent were obtained from the parents. "Written informed consent was obtained from the parents".

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Competing Interest Statement

All the authors hereby declare that we have no conflicting interests on this study. "The authors have no relevant financial or non-financial interests to disclose".

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Authors' Contribution

OAS conceptualized and designed the research work, UGA (late) and OSN supervised the work. JT, SYG and GIH, reviewed the manuscript. All authors partook in the analysis, interpretation of data obtained. All authors read and approved the final manuscript.

Data Availability

The data generated and analyzed during this study were presented in Table: 1-9.

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