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SIGNIFICANCE OF SERUM HIGH-SENSITIVITY C-REACTIVE PROTEIN IN THE DIAGNOSIS OF CO-INFECTION WITH MALARIA AND TYPHOID FEVER IN ADULTS PRESENTING WITH FEBRILE ILLNESS IN AN ENDEMIC AREA

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Abstract

Background: Malaria and typhoid fever are major causes of fever in co-endemic tropical settings where they sometimes co-exist in the same individual. Realization of the limitations of the current diagnostic tools for malaria and its overlapping infections prompted us to investigate the applicability of a novel method in the differential diagnosis of these trilateral infections.

Methods: This cross-sectional study involved an initial total of 350 febrile adult patients and 100 healthy age-and sex-matched community controls. After taking axillary temperature and collecting demographics at enrollment, 10ml peripheral blood was collected from each study subject and aliquots investigated for malaria and typhoid infections by standard microbiological methods; and ancillary hematological tests performed. A 6µl each of the harvested sera were analyzed for high-sensitivity C-reactive protein (hs-CRP) by quantitative immunoturbidimetry with the aid of Cobas CIII Autoanalyzer (Roche/Hitachi Diagnostics). The hs-CRP test diagnostic performance for malaria and/or typhoid infections was determined using MedCalc Statistical Software.

Results: The hs-CRP levels were significantly higher in the diagnosed typhoid-malaria (8.70±2.2mg/l), compared with case-malaria (7.35±1.1mg/l), case-typhoid (5.32±2.1mg/l) or controls (0.68±0.8mg/l) ($P<0.0001$ in each case). The hs-CRP diagnostic Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy were 70.59%, 97.07%, 58.38%, 98.27% and 95.61%, respectively.

Conclusion: The levels of hs-CRP were significantly higher in febrile adult patients with co-morbid malaria and typhoid infections compared to those with lone malaria fever or typhoid fever. The hs-CRP test had high levels of specificity and accuracy for co-infection with malaria and typhoid in febrile patients. Furthermore, the test was able to predict the febrile patients who were not likely to have malaria and typhoid co-infections.

Keywords: Febrile illness, Hs-CRP, Malaria, Typhoid Fever, Typhoid-malaria

Introduction

Malaria and typhoid fever (typhoid) are two of the commonest infectious diseases in the tropics where they are often endemic and constitute major public health burden. Malaria and typhoid are conditions that must be considered in pyrexia of unknown origin (PUO) in the tropics.[1] According to the recent World Malaria Report, Nigeria accounted for the highest (25%) prevalence of global malaria cases and the highest percentage (23%) of all malaria deaths worldwide in 2018.[1] The *Plasmodium falciparum* protozoan parasite causes more than 95% of malarial-associated morbidity and mortality in Nigeria.[2] On the other hand, typhoid is a worldwide human bacterial infection caused by *Salmonella enterica* serotype typhi (S. typhi). Malaria and typhoid infections continue to pose serious health challenges in developing countries often associated with poor sanitation/hygiene.

Malarial parasites and typhoidal bacteria interfere with the liver and its functions. The human C-reactive protein (CRP), a cytokines-induced and mainly liver hepatocytes-synthesized protein, is the most studied acute-phase reactant. C-reactive protein (CRP), a biomarker of infection and inflammation is released promptly in response to malaria infections,[3,4,5] other infections[6,7] and other forms of

inflammation. The serum CRP concentration reflects the inflammatory activity of a disease process. However, standard CRP assays lack the sensitivity required to determine accurately low levels of inflammation.[8]

High-sensitivity assays for CRP (hs-CRP) that are more sensitive than the original test for CRP, by allowing detection of lower range differences in CRP levels (0.3-10mg/L), have been developed for sensitive and specific quantification of CRP.[8,9,10] Previous hs-CRP studies have focused on its use in cardiovascular diseases,[10] Human Immunodeficiency Virus (HIV) infection[11] and more recently in prediabetes and/or latent tuberculosis infection in presumably 'healthy' Nigerians.[12] Information is scant on the usage of the hs-CRP method to support the diagnosis of malaria and its attendant morbidity in Nigeria. Till date, there is no established standard test for the diagnosis of co-infection with typhoid-malaria in the co-endemic population.

This study, therefore, aimed to assess the value of hs-CRP and its applicability in the differential diagnosis of the trilateral overlap of malaria and/or typhoid in a population of febrile adult outpatients attending two tertiary health care facilities in a co-endemic tropical area.

Materials and Methods

Study Design and Study Area:

This was a descriptive cross-sectional (case-control) study conducted at the University of Benin Teaching Hospital (UBTH), Benin City and Igbinedion University Teaching Hospital (IUTH) Okada; both located in Edo State, in South South Region of Nigeria.

Study Population:

Febrile adults aged 18years and older (350), attending the outpatient department (OPD) clinics of UBTH and IUTH, suspected of malaria and/or typhoid fever who have not taken antimalarial drug and/or antibiotics within two weeks of partaking in this study and have no history of typhoid fever vaccination were included, together with healthy community age- and sex-matched controls.

Inclusion criteria:

Patients: 1.With febrile illness 2.Eighteen years and older 3.Suspected of malaria or typhoid 4. Who have not taken antimalarial drug and/or antibiotics within two weeks of partaking in this study 5.With no history of typhoid fever vaccination.

Exclusion criteria:

Patients: 1.Without febrile illness 2.Less than eighteen years old 3.With underlying medical conditions. 4. Who have taken antimalarial drug and/or antibiotics within two weeks of partaking in this study 5. With history of typhoid fever vaccination.

Ethics: The primary study was approved by the University of Benin Teaching Hospital Ethical Review Board and the Igbinedion University Teaching Hospital Research & Ethical Institutional Review Board. The results of the preliminary study have been published elsewhere.[13] No formal consent was required from the volunteers as the study was conducted within a larger population-based survey on malaria control.

Data Collection:

This study was partly undertaken with retrospective analysis of routine data that were retrieved from the archives of the respective teaching hospitals. Axillary body temperature was recorded.

Clinical Laboratory Investigations:

At presentation and after study interview, 10ml of (resting) venous blood was aseptically collected from each of the febrile patients (before the administration of drugs) and members of the control group for clinical laboratory procedures.

A. Measurement of serum high-sensitivity C-reactive protein (hs-CRP)

For precise measurement of serum hs-CRP in the present study, the in vitro quantitative test was conducted using the Particle-enhanced Turbidimetric Immunoassay technique with the aid of the Cobas CIII system Auto-analyzer.[14] In brief, 6µl each of harvested serum samples of the study patients and controls were tested in batches for hs-CRP using C-reactive protein (Latex) High Sensitivity (CRPHS) (Kit Lot No: 05403138001V8) with Ref No: 05401607190, purchased from Roche Diagnostics GmbH, Sandhofer, Strasse, and run on the Cobas CIII system Autoanalyzer.[14]

B. Hematological Measurements

Hematological parameters were determined using a fully automated hematology analyzer (Sysmex ICX-ZIN), which performed complete blood counts and gave results of routine hematology laboratory variables in printout. The CD4+T lymphocyte count was assessed with the aid of the Fluorescence Activated Cell Sorter (FACS) Autoanalyzer (Becton Dickinson, Kaplan Scientific Inc., Japan).

C. Microbiological Investigations

Malaria Parasitemia Detection: Both thick and thin blood films for each study participant were prepared on clean, grease-free microscope slides. The thin films were fixed with methanol and both thick and thin films stained using 10% Giemsa solution. Both films were then examined microscopically using x100 objective under oil immersion for *Plasmodium falciparum*.

Widal's Test: Agglutination test for the detection of Salmonella typhi antibodies in the sera of study participants was performed using commercially prepared *Salmonella typhi* somatic ('O') and flagella ('H') antigens (TYDAL, Labcare Diagnostics, India). Sera with titre ≥1:80 and ≥1:160 for the 'O' and 'H' antibodies, respectively, were taken as 'Positive' for *Salmonella typhi* infection, based on the manufacturer's instructions.

Cultures for isolation of *Salmonella typhi*: To confirm the diagnosis of typhoid, blood cultures were done according to standard cultural procedures for *Salmonella typhi*, and final identification based on cultural, microscopic and biochemical characteristics as previously described.[15]

Data management and analysis:

The basic demographic and clinical laboratory raw data for the study participants were analyzed with the aid of Statistical Package for Social Sciences (SPSS) Version 23.0 Software. Results are given as mean ± standard deviation (SD) for continuous variables and compared with One-way ANOVA; categorical variables are reported as frequency or percentage (%) and tested with Chi-square. Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic accuracy of hs-CRP test were calculated using MedCalc statistical calculator (MedCalc Statistical Software; http://www.medcalc.org/calc/diagnostictest.php).
Confidence interval (CI) was set at 95% and P-value <0.05 was considered statistically significant for all analysis.

Limitations of Study:

1. Definition of 'normal' CRP levels, which vary from laboratory to laboratory and in different populations.
2. Lack of a reference 'gold standard' test for the diagnosis of typhoid-malaria.

Results

Study population:

Out of the 450 case patients and matched healthy controls initially involved in this study, an overall final total of 440 of the participants had a full set of results and were enrolled and included in the study analysis. Ten participants were excluded from the analysis because of incomplete/missing data (n = 7), undiagnosed diabetes mellitus (n = 2), or pregnancy (n = 1). Table 1 shows the basic demographics of the enrolled participants according to the study categories. A majority, 232 (52.8%) of the study population were females. The mean age of the subjects was 38.9±15.1 years at enrollment and a high majority 437 (99.4%) could read and/or write. The febrile case patients (n = 344) and the community- age- and sex- matched controls (n =96) presented homogeneity with respect to gender (P = 0.866), age (P = 0.999) and level of education (P = 0.832).

Table 1: Basic demographic data of enrolled study subjects

Variables	Febrile Patients (%) (n = 344)	Healthy Control (%) (n = 96)	Total (%)	P-Value
Gender				
Female	182 (41.4)	50 (11.4)	232 (52.8)	0.886
Male	162 (36.8)	46 (10.4)	208 (47.2)	
Total	344 (78.2)	96 (21.8)	440 (100.0)	
Age Group (years)				
18-25	54 (12.3)	16 (3.6)	70 (15.9)	0.999
26-35	92 (20.9)	25 (5.7)	117 (26.6)	
36-45	66 (15.0)	18 (4.1)	84 (19.1)	
46-55	60 (13.6)	16 (3.6)	76 (17.2)	
56-65	56 (12.7)	16 (3.6)	72 (16.3)	
≥66	16 (3.6)	05 (1.1)	21 (4.7)	
Total	344 (78.2)	96 (21.8)	440 (100.0)	
Level of Education				
Illiterate	02 (0.4)	01 (0.2)	03 (0.6)	0.832
Primary	84 (19.1)	20 (4.5)	104 (23.6)	
Secondary	130 (29.5)	36 (8.2)	166 (37.7)	
Tertiary	128 (29.1)	39 (8.9)	167 (38.0)	
Total	344 (78.2)	96 (21.8)	440 (100.0)	

Clinical laboratory measurements:

The outcome of the measured clinical laboratory parameters of the participants according to the diagnosed infection status are presented in Table 2. Prevalence rate of malaria parasitemia 195 (56.7%), *Salmonella typhi* 42 (12.2%) and concurrent typhoid-malaria 19 (5.5%) were recorded among the febrile cases. (Table 2). The study patients have significantly elevated body temperature and total WBC counts compared with controls (P<0.0001 in each case). Conversely, hematocrit level and CD4+T cells were significantly lower in the study patients when compared with controls (P<0.0001 in each case) (Table 2).

Association of hs-CRP levels with infection status:

The hs-CRP responses in case-malaria patients (7.35±1.1mg/l) were significantly higher than patients with typhoid fever (5.32±2.1mg/l) but lower than patients with typhoid-malarial infection (8.70±2.2mg/l), while case controls recorded low hs-CRP (0.68±0.8mg/l) (P<0.0001), resulting in a quadratic association between typhoid-malarial infection and hs-CRP (Table 2).

Table 2: Comparison of measured clinical parameters between infected febrile case patients and controls

Parameters	Healthy Control (n=96)	Malaria (n=195)	Typhoid (n=42)	Typhoid-malaria (n=19)	P-value
Temperature (range) ^{0}C	36.6-37.5[a]	38.9-40.5[b]	38.2-40.2[c]	39.2-40.7[d]	<0.0001
Hs-CRP level (mg/l)					
mean±SD	0.68±0.8[a]	7.35±1.1[b]	5.32±2.1[c]	8.70±2.2[d]	<0.0001
median	1.1	6.8	5.8	8.1	
IQR	(0.3-2.1)	(5.5-7.8)	(6.1-7.2)	(8.0-9.5)	
Hb±SD (g/dl)	12.6±1.2	12.1±2.1	12.3±1.5	11.6±1.7	0.062
HCT±SD (%)	36.7±0.7[a]	32.8±2.9	32.9±2.8	31.8±3.6	<0.0001
RBC (median) X 10^{12}/L	5.4	5.2	4.8	5.1	0.643
WBC (range) X 10^3/L	(4.3-4.9)[a]	(5.8-7.3)[b]	(5.3-6.5)[c]	(8.9-9.7)[d]	<0.0001
CD4+T±SD (cells/µl)	895±205.3[a]	481±73.1[bc]	520±55.6[b]	408±31.3[c]	<0.0001
Lymph±SD (%)	36.1±0.7	36.3±1.7	35.6±2.8	35.8±3.2	0.108
Mon±SD (%)	5.9±2.9	5.3±3.3	5.8±2.2	6.0±1.9	0.345

Key: Hs-CRP- High-sensitivity C-reactive protein; Hb- Haemoglobin; HCT- Haematocrit; RBC- Red blood cell; WBC- White blood cell; Lymph- Lymphocytes; Mon- Monocytes; SD- Standard deviation
N.B: Groups that share same letter are not significantly different at P<0.05

Univariate Analysis of hs-CRP levels in case patients:

The distribution of hs-CRP levels across the different febrile infection groups are shown in Table 3. Aggregated, the recorded hs-CRP levels were low (≤0.30mg/l) in 16 (4.6%) patients, medium (0.31-6.50mg/l) in 59 (17.2%), high (6.51-9.99mg/l) in 164 (47.7%) and relatively higher (≥10.00mg/l) in 17(4.9%) of the febrile patients (Table 3). Our results indicate that the median hs-CRP concentration is lowest in the control group (data not shown). Only 3 (0.9%) and 2 (0.6%) of the patients with diagnosis of malaria and typhoid respectively, had increased hs-CRP levels ≥10.00mg/l (Q4 quartile). Increased hs-CRP levels ≥10.00mg/l were strongly associated with febrile patients with concomitant typhoid and malaria (OR 75.00 [CI 3.78 – 1486.87], P<0.05).

Test quality of hs-CRP levels for differentiating between febrile infections:

To evaluate the utility of hs-CRP in distinguishing between malaria, typhoid or typhoid-malaria infections, the sensitivity, specificity, PPV, NPV and accuracy of the test at cut-offs of 0.31mg/l, 6.51mg/l and 10.00mg/l were calculated (Table 4). In typhoid-malaria patients, the values at hs-CRP cut-off of 10.00mg/l were 70.59% (CI 64.04% - 89.69%), 97.07% (CI 94.06% - 98.81%), 58.38% (CI 38.86% - 75.59%), 98.27% (CI 96.45% - 99.16%) and 95.61% (CI 92.33% - 97.77%), respectively.

Table 3: Univariate analysis of the association between hs-CRP levels and diagnosed case patients.

Hs-CRP level (mg/l)	Malaria		OR (95% CI)	P-value	Typhoid		OR (95% CI)	P-value	Typhoid-malaria		OR (95% CI)	P-value
	No (%)	Yes (%)			No (%)	Yes (%)			No (%)	Yes (%)		
Q1 (≤0.3) n = 16 (4.6)	8 (2.3)	8 (2.3)	1		8 (2.3)	8 (2.3)	1		16 (4.6)	0 (0.0)	1	
Q2 (0.31-6.50) n = 59 (17.1)	29 (8.4)	30 (8.7)	1.03 (0.34-3.12)	>0.05	32 (9.3)	27 (7.8)	0.84 (0.27-2.55)	>0.05	57 (16.6)	2 (0.6)	1.43 (0.06-31.39)	>0.05
Q3 (6.51-9.99) n = 164 (47.7)	10 (2.9)	154 (44.7)	15.40 (4.77-49.63)	<0.0001*	159 (46.2)	5(1.4)	0.03 (0.01-0.12)	<0.0001*	159 (46.2)	5 (1.4)	1.14 (0.06-21.51)	>0.05
Q4 (≥10.00) n = 17 (4.9)	14 (4.1)	3 (0.9)	0.21 (0.04-1.05)	>0.05	15 (4.4)	2 (0.6)	0.13 (0.02-0.78)	<0.05*	5 (1.4)	12 (3.5)	75.00 (3.78-1986.87)	<0.05*
Total	**61 (17.7)**	**195 (56.7)**			**214 (62.2)**	**42 (12.2)**			**237 (68.9)**	**19 (5.5)**		

*Significant at P<0.05; OR – Odds Ratio; Q – Quartile; CI – Confidence Interval

Table 4: Test quality of hs-CRP levels for the differentiation between malaria, typhoid and typhomalaria

	Malaria			Typhoid			Typhoid-malaria		
Hs-CRP cut-off (mg/l)	**0.31**	**6.51**	**10.00**	**0.31**	**6.51**	**10.00**	**0.31**	**6.51**	**10.00**
Sensitivity (%)	77.92	86.74	17.65	14.17	3.87	11.76	7.60	9.39	70.59
(95% CI)	(72.13-83.00)	(80.92-91.32)	(3.80-43.43)	(10.01-19.23)	(1.57-7.81)	(1.48-36.44)	(4.64-11.61)	(5.57-14.61)	(64.04-89.69)
Specificity (%)	50.00	49.33	19.67	50.00	53.33	83.26	100.00	97.33	97.07
(95% CI)	(24.65-75.35)	(37.58-61.14)	(14.82-25.28)	(24.65-75.35)	(41.45-64.95)	(77.91-87.77)	(79.41-100.00)	(90.70-99.68)	(94.06-98.81)
PPV(%)	67.11	80.51	22.34	3.79	1.14	8.90	100.00	17.01	58.38
(95% CI)	(55.44-76.99)	(76.64-83.88)	(9.32-44.59)	(2.16-6.57)	(0.53-2.42)	(2.51-27.01)	(82.17-100.00)	(4.63-46.39)	(38.86-75.59)
NPV(%)	63.36	60.66	15.42	80.74	79.97	87.17	94.90	94.86	98.27
(95% CI)	(50.07-74.88)	(49.88-70.48)	(11.51-21.36)	(71.92-87.28)	(76.33-83.18)	(84.98-89.07)	(94.72-95.07)	(94.56-95.15)	(96.45-99.16)
Accuracy (%)	65.83	75.78	18.52	45.63	47.30	74.54	94.92	92.50	95.61
(95% CI)	(59.67-71.62)	(70.06-80.90)	(13.96-23.83)	(39.41-51.95)	(41.05-53.61)	(68.74-79.76)	(91.55-97.23)	(88.56-95.41)	(92.33-97.77)

Discussion

This case-control study in two tertiary health institutions in Nigeria showed that out of a total of 344 febrile adults screened by conventional microbiological techniques, 195 (56.7%) were diagnosed positive for malaria, while 42(12.2%) were positive for typhoid, and a subset of the febrile adults 19 (5.5%) harbored malaria and typhoid infections concurrently. The follow-up assessment in this study using the highly sensitive hs-CRP immunoassay showed that the malaria cases produced relatively higher hs-CRP levels (7.35±1.1mg/l) compared with the typhoid cases (5.32±2.1mg/l) but significantly lower than the typhoid-malaria cases (8.7±2.2mg/l); the healthy control individuals produced consistently much lower hs-CRP (0.68±0.8mg/l) when compared to the infected groups (P<0.0001 in each case). This study also revealed that hs-CRP cut-off value 10.00mg/l was associated with the highest risk of typhoid-malaria infection in the study area.

The findings in this work are supported by a similar previous study conducted in Nigeria on the concurrence of malaria and typhoid infections among 300 febrile patients in Jos, Nigeria, that reported prevalence rate for concurrent malaria and typhoid (5.6%), malaria (54%) or typhoid fever (42%).[16] In another study of febrile patients in Calabar, Nigeria, 80.8% tested positive for malaria, 46.8% had typhoid, while 0.8% were diagnosed with typhoid and malaria co-infection.[17] However, an Indian study to evaluate the efficacy of various tests for diagnosis of typhoid and malaria co-infection among preponderantly male febrile patients reported varying prevalence rates for the three infections, depending on the laboratory technique employed in the diagnosis.[18] The apparent discrepancies in these reports could be attributed to the population studied and, importantly, the varying laboratory techniques used in the diagnosis. It is noteworthy that none of these previous tropical studies utilized the highly sensitive hs-CRP immunoassay method as deployed in the present work.

In our study, significant differences in laboratory findings of malaria, typhoid and typhoid-malaria cases were found in WBC, CD4+T, hematocrit and hs-CRP values. Highest levels of hs-CRP were consistently observed in typhoid and malaria co-infected patients when compared with malaria and typhoid mono-infections. In the univariate analysis of our findings, none (0.0%) of the typhoid-malaria cases had low (≤ 0.3mg/l) whereas 12 (3.5%) produced hs-CRP ≥ 10 mg/l, the level associated with high risk of typhoid-malaria in this study. The validity of a diagnostic tool mainly depends on its sensitivity and positive predictive value (PPV). The sensitivity of hs-CRP as a diagnostic tool for case typhoid-malaria in the present study is 70.59% with a 95% CI of 64.04% - 89.69%. This shows that the hs-CRP test is only fairly sensitive and able to correctly identify individuals who actually have typhoid-malaria. The relatively lower PPV shows that hs-CRP has a limited (58.38%) ability to accurately determine the proportion of those who are truly positive for typhoid-malaria. However, the high values of NPV and accuracy of elevated hs-CRP imply that elevated hs-CRP has high ability to accurately determine the proportion of those who are truly negative for typhoid-malaria. Based on these findings, hs-CRP levels less than10mg/l may be used in excluding typhoid-malaria in febrile adults.

Taken together, hs-CRP levels at the diagnostic threshold of 10mg/l had a limited ability to identify typhoid-malaria in the present study.

The hs-CRP testing in typhoid-malaria infection might not be useful yet for diagnostic purposes in clinical settings. Further prospective studies in larger cohorts are necessary so as to provide information regarding the value of serial

measurements of serum hs-CRP before and after infection, which could further indicate the diagnostic relevance of hs-CRP in these overlapping infections.

Conclusion

Our results have shown that malaria is more likely the cause of fever than typhoid or typhoid-malaria in this region. The hs-CRP immunoassay revealed remarkably elevated immune response in a subset of febrile adults diagnosed with typhoid-malaria. The study cut-off value of 10.0mg/l was found associated with high risk of typhoid-malaria infection in the study geographic area. However, the high specificity and high NPV of the hs-CRP test indicate that it could be useful in excluding typhoid-malaria co-infections. Therefore, a single hs-CRP test is not a reliable option in the differential diagnosis of the overlapping triad of malaria and/or typhoid fever.

Nevertheless, our data suggest that the hs-CRP test may serve as an effective supplementary diagnostic biomarker for concurrent malaria and typhoid infections in febrile illness, especially in co-endemic settings. However, factors such as hs-CRP assay standardization must be addressed adequately as 'normal' hs-CRP levels vary from laboratory to laboratory and in different populations.

References

1. World Health Organization. World malaria report. Geneva. 2019.
2. Nigeria National Malaria Elimination Programme, LSHTM and KEMRI-Wellcome Trust Research Programme. Nigeria: A profile of malaria control and epidemiology, 2018 Overview. A report prepared for the Federal Ministry of Health, Nigeria and the Department for International Development, UK; 2018.
3. McGuire W, D'Alessandro U, Olaleye B.O, Thomson MC, Langerock P, Greenwood BM, Kwiatkowski D. C-reactive protein and haptoglobin in the evaluation of a community-based malaria control programme. Tran R Soc Trop Med Hyg. 1996; 90(1): 10-4.
4. Paul R, Sinha PK, Bhattacharya R, Banerjee AK, Raychaudhuri P, Mondal J. Study of C- Reactive protein as a prognostic marker in malaria from eastern India. Adv Biomed Res. 2012; 1:41.
5. Gillespie SH, Dow C, Raynes JG, Behrens RH, Chiodini PL, McAdam KP. Measurement of acute phase proteins for assessing severity of *Plasmodium falciparum* malaria. J Clin Pathol. 1991; 44 (3): 228–31.
6. Clyne B, Olshaker JS. The C- Reactive Protein. J Emerg Med. 1999; 17(6):1019–25.
7. West BA, Peterside O, Ugwu RO, Eneh AU. Prospective Evaluation of the usefulness of C-reactive protein in the diagnosis of neonatal sepsis in a sub-Saharan African region. Antimicrobial Resistance and Infection Control. 2012; 1:22.
8. Ockene IS, Matthews CE, Rifai N, Ridker PM, Reed G, Stanek E. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. Clin Chem. 2001; 47:444-50.
9. Ledue TB, Rifai N. High sensitivity immunoassays for C-Reactive protein: promises and pitfalls. Clinical Chemistry and Laboratory Med. 2005; 39(11):185
10. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003; 107:363-69.
11. Vishwanath A, Quaiser S, Khan R. Role of high-sensitivity C-reactive protein measurement in HIV patients. Indian J Sexually Transmitted Diseases and AIDS. 2016; 37(2): 123-28.
12. Akinshipe BO, Yusuf EO, Ehiaghe AF, Egunjobi TO, Yusuf OA. Elevated high-sensitivity C-reactive protein among apparently healthy adults with concomitant prediabetes and latent tuberculosis infection in Nigeria. Int J Res Med Sci. 2021; 9(2): 338-46.
13. Yusuf, E. O., Akinshipe, B. O., and Airauhi, L. U.: Some Haematological and Biochemical Changes Associated With Malaria Parasitaemia In Adults Attending Tertiary Out-Patient Clinics In Edo State, Nigeria BJMLS. 2020; 5(2): 31 – 40.
14. Roche Cobas c111 User Manual. https://www.scribd.com/doc /9125231/Roche-cobas c111-user-Manual.
15. Cheesbrough, M. District Laboratory Practice in Tropical Countries Part 1, 2nd edition, Cambridge University Press, Cambridge, UK. 2005; 454
16. Ukaegbu CO, Nnachi AU, Mawak JD, Igwe CC. Incidence of concurrent malaria and typhoid fever infection in febrile patients in Jos, Plateau state, Nigeria. Int J Scientific and Technology Res. 2014; 3: 157-61.
17. Orok DA, Usang AI, Ikpan OO, Duke EE, Eyo EE, Edadi UE, Ati BU, Udida JA. Prevalence of Malaria And Typhoid Fever Co-Infection Among Febrile Patients Attending College Of Health Technology Medical Centre In Calabar, Cross River State, Nigeria. Int. J. Curr. Microbiol. App. Sci. 2016; 5(4): 825-35.
18. Sharma B, Matlani M, Gaind R, Pandey K. "Malaria and typhoid co-infection in India. A diagnostic difficulty". Journal of Dental and Medical Sciences. 2016; 15(9): 101-4.