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Surrogate Inflammatory Markers and Some Correlates in Pre-dialysis Chronic Kidney Disease Patients: a cross-sectional study

Mamven M[1], Ucha I[2], Adejumo O[3]ID

[1]*Department of Medicine, College of Health Sciences, University of Abuja, FCT, Nigeria*
[2]*Department of Medicine, University of Abuja Teaching Hospital Gwagwalada, Nigeria*
[3]*Department of Medicine, University of Medical Sciences Ondo State, Nigeria*

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Abstract

Objective: Chronic kidney disease is characterized by a state of chronic inflammation which is associated with poor cardiovascular disease outcomes. The study determined the prevalence of elevated neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as surrogate markers of inflammation and their association with some cardiovascular risk factorsamong pre-dialysis CKD patients.

Method: This was a cross-sectional study to determine and compare the prevalence of elevated NLR and PLR. The correlation between these surrogate inflammatory markers and some cardiovascular risk factors was determined. Data were analyzed using SPSS version 21 software. P-value of < 0.05 was taken as significant.

Results: This study involved 51 pre-dialysis CKD patients and 51controls with mean ages of 50.96±11.42 years and 48.31±9.83 years, respectively. The prevalence of elevated NLR was significantly higher in the CKD group (35.3% vs13.7%; P=0.010). In the CKD group, there was significant negative correlation between NLR and eGFR (r= -0.393; P=0.004), hemoglobin concentration (r= -0.543; P=<0.001) and HDL (r= -0.292; P=0.037). There was significant positive correlation between NLR and PLR (r=0.669; P=<0.001), TC:HDL (r=0.334; P=0.017), AIP(r=0.289; P=0.042) and LDL:HDL (r=0.320; P=0.020). There was significant positive correlation between PLR, NLR (r=0.695; P=<0.001) and AIP (r=0.283; P=0.047). There was significant negative correlation between PLR and estimated GFR (r=-0.448; P=0.001), hemoglobin concentration (r= -0.596; P=<0.001), serum albumin (r= -0.388; P=0.005), serum HDL-C (r= -0.387; P= 0.005).

Conclusion: NLR and PLR were significantly higher in pre-dialysis CKD patients and were associated with cardiovascular risk. They should be routinely used to identify those with high cardiovascular risk.

Keywords: neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, cardiovascular, risk factor,pre-dialysis, chronic kidney disease

Plain English Summary

Chronic kidney disease is characterized by chronic inflammation which may adversely affect the cardiovascular outcomes of patients with this disease. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are cheap alternatives that can be used to assess inflammation. Inflammation was assessed using this method in those with chronic kidney disease and those with normal kidney function. Their association with cardiovascular risk factors was also determined. It was found that these ratios were significantly elevated in chronic kidney disease patients compared with those with normal kidney function. In addition, these ratios were closely related to some cardiovascular risk factors. These ratios could help identify chronic

Correspondence:
Mamven, Manmak
Department of Medicine, College of Health Sciences, University of Abuja,
FCT, Nigeria
manmakm@yahoo.com

kidney disease patients with high cardiovascular risks so that intervention can be promptly commenced. These interventions will include prompt correction of dyslipidemia with statins in patients with chronic kidney disease.

Background

Cardiovascular disease is a major cause of morbidity and mortality in chronic kidney disease (1). CKD patients are more likely to die from cardiovascular disease than to progress to end-stage renal disease (2). The high prevalence of both traditional and non-traditional cardiovascular risk factors in CKD patients contributes significantly to this cardiovascular disease burden (3). The traditional risk factors include hypertension, diabetes mellitus, dyslipidemia, and age while the non-traditional risk factors include hyperparathyroidism, albuminuria, homocysteinemia, inflammation, and anemia (4, 5).

Inflammation contributes significantly to cardiovascular disease in CKD (6). CKD is referred to as a chronic inflammatory state (7). The causes of inflammation in CKD include reduced elimination of cytokines and increased cytokine production, frequent infection, oxidative stress, vitamin D deficiency, intestinal dysbiosis, periodontal disease, metabolic acidosis, and dialysis-related factors (7, 8). The consequences of inflammation favor atherosclerosis which accounts for an increased risk of cardiovascular disease (8).

Different markers of inflammation such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha have been identified in CKD (9, 10). However, these are not routinely assessed in the management of CKD especially in low-resource countries because of cost, unavailability of kits, and lack of expertise. Over the years, neutrophil-lymphocyte (NLR) and platelet-lymphocyte ratios (PLR) have emerged as useful inflammatory markers in chronic conditions such as cancers and CKD (9, 10, 11, 12, 13). These ratios can easily be derived from parameters available when a full blood count is done either manually or by automation. These ratios can easily be calculated for CKD patients and used in cardiovascular risk stratification, especially in low-resourcecountries. Identification of factors associated with an increase in these ratios in CKD patients may serve as a potential therapeutic target aimed at reducing their cardiovascular risk and improving their overall outcomes. In addition, there is limited information about these cardiovascular markers among pre-dialysis CKD patients in Nigeria. This study determined the prevalence of elevated NLR and PLR and some associated cardiovascular factors in a population of pre-dialysis CKD patients attending the University of Abuja Teaching Hospital in Nigeria.

Methods

This was a cross-sectional study that was carried out at the University of Abuja Teaching Hospital (UATH), Gwagwalada; a tertiary health center in the Federal Capital Territory (FCT).

Sample size determination

The sample size was calculated using the Leslie-Kish formula for a cross-sectional study (14).

$N = (Z1\text{-}a/2)^2 * P (1\text{-}P)/d^2$. N=minimum sample size; Z1-a/2= level of significance at 95% confidence interval = 1.96; P= available prevalence of elevated NLR (19. 7%) from a previous study done among CKD patients (15); d = degree of precision limit required =5 % (0.05) so n = 243. For small finite population, the corrected sample size is; Nf = n/1+n-1/N. Where N= average number of pre-dialysis CKD patients seen at nephrology clinics (from clinic register) in the hospital in the last 6 months. N = 60 pre-dialysis patients in the last 6 months. n= calculated sample size (243), Nf = corrected sample size, which is 243/ (1 + {243-1/60}) = 243 / 5.03=48.

Study participants

A total of 51 pre-dialysis CKD patients and 51 healthy controls without CKD who fulfilled the inclusion criteria were consecutively recruited for the study over six months. Inclusion criteria were consenting adults patients of age 18-65 years with estimated glomerular filtration rate (eGFR) of < 60mls/min/1.73m^2, and those yet to commence renal replacement therapy (RRT). The control group was consenting individuals without a history suggestive of CKD; absence of urinary abnormality on examination; and presence of eGFR of > 60mls/min/1.73m^2. CKD patients with inflammatory gastrointestinal disease, dementia, chronic liver disease, nephrotic syndrome, ongoing infection, chronic infection such as tuberculosis, and those on steroid therapy were excluded.

Data collection

Questionnaires were administered by the researchers to obtain a history of the study participants and a physical examination was

conducted thereafter. Anthropometric measurements were taken. The body weight was determined using a standard weighing scale with the participantswearing light clothing and without shoes. Measurement was taken to the nearest 0.5kg. The height was taken in meters to the nearest 0.5m using a graduated height scale. Participants were in erect posture and their back against a straight wall without headgear or shoes. Waist circumference (WC) in centimeters (cm) was taken using a tape rule at the level of the umbilicus.Body mass index (BMI) was calculated using the formula: BMI= Weight (kg)/Height^2 (m^2). Fasting blood samples were taken for fasting serum lipid, automated full blood count, serum albumin, and creatinine. Serum total cholesterol (TC) and triglyceride (TG) were determined by the enzymatic spectrophotometric method (16). Serum high-density lipoprotein-cholesterol (HDL-C) was determined after precipitating other lipoproteins as reported by Burstein *et al* (17) while low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation (18).

LDL-C =TC – HDL-C – (TG /2.2) (18). Serum creatinine was measured using the Jaffe reaction method (19). The estimated eGFR was calculated using the CKD-EPI formula. Full blood count with differentials was done using the Beckman Coulter method of counting and sizing, in combination with an automatic diluting and mixing device for sample processing and a single beam photometer for hemoglobinometry. The Kidney Disease Improving Global Outcomes (KDIGO) guideline was used to stage CKD (20). Absolute neutrophil and lymphocyte counts were obtained from the full blood count by multiplying the percentage neutrophil and lymphocyte count respectively by the total white cell count. The atherogenic index of plasma (AIP) are derived by calculating the Log (TG/HDL-C) (21). The NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count. The PLR was calculated by dividing absolute platelet count by absolute lymphocyte count. An NLR and PLR values of >1.86 and >160 respectively, were considered elevated (10, 15).

Data Analysis

Data from the study were entered and analyzed using IBM SPSS version 21 software. Discrete variables were presented as frequencies and percentages. Continuous variables were presented as means with standard deviation for normally distributed data while median with interquartile range was used for skewed data. Independent t-test was used to compare means of normally distributed continuous while the Mann-Whitney U test was to compare the median of skewed continuous variables. Pearson's and Spearman's correlations were used to assess the association between NLR, PLR, and some cardiovascular risk factors for normally distributed variables and skewed variables, respectively in the CKD group. A P-value of <0.05 was regarded as significant.

Results

There were 51 pre-dialysis CKD patients and 51 controls in the study. There was no significant difference in the mean age of the groups of study participants. The prevalence of elevated NLR was significantly higher in the CKD patients compared to the controls (35.3% vs 13.7%; P=0.010). The prevalence of elevated PLR was significantly higher in the CKD patients compared to the controls (74.5% vs 23.5%; P=< 0.001). The median values of NLR, PLR, serum TG, serum LDL-C, TC:HDL-C, TG:HDL-C, LDL-C, TG, and AIP were significantly higher in the CKD group compared to the control group. The mean serum albumin, hemoglobin concentration, and median value of eGFR were significantly lower in the CKD group compared to the control group. (Table 1)

Table 1: Comparison of Parameters between CKD and Control Groups

Parameter	CKD group (n=51)	Control group (n=51)	P-value
*Age (years)	50.96 (11.42)	48.31 (9.83)	0.213
Elevated NLR	18(35.30%)	7(13.7%)	0.010
Elevated PLR	38(74.50%)	13(23.50%)	<0.001
**NLR	1.54 (0.72)	1.02 (0.38)	<0.001
**PLR	207.60 (126.44)	91.67 (77.83)	<0.001
*Serum Albumin (g/L)	34.77 (7.86)	39.45 (5.83)	0.001
* Serum TC (mmol/L)	4.20 (1.48)	4.46 (0.69)	0.250
**Serum TG (mmol/L)	1.60 (0.53)	1.07 (0.37)	<0.001

**Serum HDL-C (mmol/L)	0.81 (0.53)	1.28(0.62)	<0.001
**Serum LDL-C (mmol/L)	2.65 (1.28)	2.56 (0.63)	0.662
**TC:HDL-C	5.00 (3.28)	3.20 (1.54)	<0.001
**TG:HDL-C	1.99 (1.66)	0.72 (0.37)	<0.001
**LDL-C:HDL-C	3.17 (3.02)	1.92 (1.48)	<0.001
**AIP	0.30 (0.35)	-0.14(0.22)	<0.001
*Hemoglobin concentration (g/dL)	9.52 (1.89)	12.94 (1.74)	<0.001
**Estimated GFR (mls/min/1.72m^2)	24.00(27.00)	92.00(17.00)	<0.001

* Normally distributed data expressed as mean (standard deviation) ** skewed data expressed as median (interquartile range)
HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol), TG (triglyceride), TC (total cholesterol), AIP (atherogenic index of plasma), GFR (glomerular filtration rate)

Among the CKD group, the mean hemoglobin concentration, median serum HDL-C and estimated GFR was significantly lower in the CKD patients with high NLR compared with those with normal NLR. Also, the median TC:HDL-C, LDL-C, HDL-C, and PLR were significantly higher in the CKD patients with high NLR compared with those with normal NLR.(Table 2)

Table 2: Comparison of Parameters between CKD Patients with High NLR and Normal NLR

Parameter	High NLR (n=18)	Normal NLR (n=33)	P-value
*Age (years)	52.17 (8.04)	50.30 (12.97)	0.543
*Hemoglobin concentration (g/dL)	8.53 (1.63)	10.06 (1.83)	0.004
* Serum TC (mmol/L)	4.31 (1.50)	4.14 (1.48)	0.438
**Serum HDL-C (mmol/L)	0.69 (0.37)	0.91 (0.33)	0.045
**Serum LDL-C (mmol/L)	2.84 (1.24)	2.54 (1.31)	0.416
**Serum TG (mmol/L)	1.74 (0.54)	1.53 (0.51)	0.161
* Serum Albumin (g/L)	33.22 (8.22)	35.61 (7.65)	0.160
**AIP	0.46 (0.37)	0.26 (0.23)	0.934
**TG:HDL-C	4.25 (4.55)	2.03 (1.28)	0.097
**TC:HDL-C	8.94 (7.22)	5.22 (2.72)	0.031
**LDL:HDL-C	6.04 (5.18)	3.31 (2.24)	0.031
**Estimated GFR (mls/min/1.72m^2)	19 (7.25)	29.0 (34.00)	0.033
**PLR	275.19 (100.37)	173.85(102.61)	0.003

* Normally distributed data expressed as mean (standard deviation) ** skewed data expressed as median (interquartile range)
HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol), TG (triglyceride), TC (total cholesterol), AIP (atherogenic index of plasma), GFR (glomerular filtration rate), PLR (platelet lymphocyte ratio)

The mean hemoglobin concentration and serum albumin were significantly lower in the CKD patients with elevated PLR. The median value of NLR was significantly higher in CKD patients with high PLR (Table 3)

Table 3: Comparison of Parameters between CKD patients with High PLR and Normal PLR

Parameter	High PLR (n=38)	Normal PLR (n=13)	P-value
*Age (years)	52.68 (9.61)	45.92 (14.89)	0.146
*Hemoglobin	9.14 (1.79)	10.64 (1.82)	0.017
*Serum TC (mmol/l)	4.30 (1.68)	3.89 (0.48)	0.181
**Serum HDL-C (mmol/l)	0.66 (0.76)	0.88 (0.44)	0.935
**Serum LDL-C (mmol/l)	2.46 (1.13)	2.17 (1.06)	0.815
**Serum TG (mmol/l)	1.62 (0.57)	1.54 (0.40)	0.513
**Serum Albumin(g/L)	33.26 (7.74)	39.15 (6.67)	0.015

**AIP	0.31 (0.54)	0.27 (0.27)	0.867
**TG:HDL-C	2.03 (4.31)	1.87 (1.39)	0.806
**TC:HDL-C	6.73(5.78)	4.69 (3.37)	0.229
**LDL:HDL-C	4.42 (3.92)	2.75 (2.93)	0.229
**Estimated GFR (mls/min/1.72m^2)	19.00 (7.25)	28.00 (34.50)	0.089
**NLR	1.94 (0.88)	1.04 (0.47)	0.005

* Normally distributed data expressed as mean (standard deviation)
** Skewed data expressed as median (interquartile range)
NLR (neutrophil lymphocyte ratio), HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol), TG (triglyceride), TC (total cholesterol), AIP (atherogenic index of plasma), GFR (glomerular filtration rate), PLR (platelet lymphocyte ratio).

In the CKD group, there was significant negative correlation between NLR and eGFR (r= -0.393; P=0.004), hemoglobinconcentration (r= -0.543; P=<0.001) and HDL-C (r= -0.292; P=0.037). There were significant positive correlations between NLR and PLR (r=0.669; P=<0.001), TC:HDL-C(r=0.334; P=0.017), AIP(r=0.289; P=0.042) and LDL-C:HDL-C(r=0.320; P=0.020). (Table 4)

TABLE 4: Correlation between NLR and other Parameters

Parameter	r-coefficient	P-value
Age (years)	0.019	0.897
Estimated GFR (mls/min/1.72m^2)	-0.393	0.004
Haemoglobin concentration (g/L)	-0.543	<0.001
PLR	0.695	<0.001
Serum Albumin (g/L)	-0.215	0.130
Serum total cholesterol (mmol/l)	0.122	0.395
Serum triglyceride (mmol/l)	0.197	0.166
Serum HDL-C(mmol/l)	-0.315	0.024
Serum LDL-C(mmol/l)	0.168	0.238
TC:HDL-C	0.335	0.017
TG:HDL-C	0.278	0.048
Atherogenic Index of Plasma	0.289	0.042
LDL-C:HDL-C	0.320	0.022

NLR (neutrophil lymphocyte ratio), PLR (plasma lymphocyte ratio), HDL-C (high density lipoprotein-cholesterol), LDL-C (low density lipoprotein-cholesterol), GFR (glomerular filtration rate)

In the CKD group, there was significant positive correlation between PLR, NLR (r=0.695; P=<0.001) and AIP (r=0.283; P=0.047). There was significant negative correlation between PLR and estimated GFR (r= - 0.448; P=0.001), hemoglobin concentration (r= -0.596; P=<0.001), serum albumin (r= -0.388; P= 0.005), serum HDL-C (r= -0.387; P= 0.005), (Table 5)

TABLE 5: Correlation between PLR and other Parameters

Parameter	r-coefficient	P-value
Age	0.084	0.557
NLR	0.695	<0.001
Estimated GFR (mls/min/1.72m^2)	-0.448	0.001
Hemoglobin concentration (g/L)	-0.596	<0.001
Serum Albumin (g/L)	-0.388	0.005
Serum total cholesterol (mmol/l)	-0.196	0.169
Serum triglyceride (mmol/l)	0.107	0.457

Serum HDL-C (mmol/l)	-0.387	0.005
Serum LDL-C (mmol/l)	-0.009	0.950
TC:HDL-C	0.273	0.053
TG:HDL-C	0.272	0.054
Atherogenic Index of Plasma	0.283	0.047
LDL-C:HDL-C	0.248	0.050

NLR (neutrophil lymphocyte ratio), PLR), HDL-C (high density lipoprotein-cholesterol), LDL-C (low densitylipoprotein-cholesterol), GFR (glomerular filtration rate).

Discussion

This study determined the prevalence of elevated NLR and PLR and associated factors in a population of pre-dialysis CKD at the University of Abuja Teaching Hospital in Nigeria. The prevalence of elevated NLR was 35.3% among the pre-dialysis CKD group which was significantlyhigher than the 13.7% observed in the control. The median value of NLR was also significantly higher in pre-dialysis CKD compared with the control group with normal renal function. This is similar to a similar report from a previous study by Okyay et al (11). These findings showed that CKD is associated with inflammation even before the disease progresses to end-stage renal disease.

The prevalence of elevated NLR in our study is lower than 64.4% reported by Ogiator et al (22). The lower prevalence seen in our study may be partly explained by the fact that our study was conducted among pre-dialysis CKD compared to the study by Ogiator et al (22) that was conducted among end-stage renal disease patients. In addition, elevated NLR was defined in our study using a cut-off of greater than 1.86 compared to the study by Ogiator et al (22) that used a lower cut-off of greater than 1.5. The prevalence of elevated NLR in our study is higher than 19.7% reported by Uduagbamen et al (15) in a study that was conducted among pre-dialysis CKD wherea cut-off of ≥ 3 was used to define elevated NLR. However, the study by Uduagbamen et al (15) involved early stages of CKD (stages 1-4) unlike our study which involved stages 3-5. This may partlyexplain the higher prevalence of elevated NLR in our study compared to that of Uduagbamen et al (15).

In the same vein, the median value of PLR was significantly higher in the CKD group compared with the control group with normal renal function. The prevalence of elevated PLR was 74.5% among the pre-dialysis CKD group which was significantly higher than the 23.5% observed in the control. This also corroborates the fact that CKD is associated with inflammation. The prevalence observed in this present study is lower than 26.2% reported by Uduagbamen et al (15) where a similar cut-off value was used to define elevated PLR. As noted earlier, this difference may be partly because Uduagbamen et al (15) studied early CKD patients compared to our study despite using a similar cut-off value of greater than 160 to define elevated PLR.

The NLR and PLR are simple biomarkers of systemic inflammation that have been extensively studied in several pro-inflammatory states like cancers and are now being investigated and used in CKD (9, 10, 11, 12, 13). Inflammation and immune cells have been implicated in the development and progression of CKD to end-stage renal disease (23, 24). These inflammatory markers are associated with poor renal outcomes such as progression to end-stage renal disease and death among CKD patients (10, 25). In a systematic review and meta-analysis by Zhao et al (26), NLR was found to be a predictor of all-cause mortality and cardiovascular events in CKD patients. Both NLR and PLR are simple, inexpensive, and readily available measures of systemic inflammation. These markers have been reported to be significantly correlated with conventional inflammatory markers such as C-reactive proteins and interleukins (10, 11). Hence, both NLR and PLR could be used as alternative markers of inflammation in low-resource countries like Nigeria.

Both NLR and PLR showed a significant negative correlation with eGFR in the pre-dialysis CKD group. This showed that these inflammatory markers increased with worsening renal function which is in keeping with some previous reports (10, 15, 25). This is partly due to the fact that as the GFR decline, there is increased production of pro-inflammatory mediators and reduced clearance of these mediators. There was no significant correlation between serum albumin and NLR in the pre-dialysis CKD group. However, there was a significant negative correlation between serum albumin and PLR which is not surprising because serum albumin is an inflammatory marker in CKD.

There was a significant negative correlation between hemoglobin, NLR, and PLR. This is similar to reports from previous studies (10, 11). Anemia is a cardiovascular risk factor in CKD patients that predicts mortality (27, 28). The relationship between hemoglobin concentration and the inflammatory markers in this study may be partly explained by the fact that inflammation contributes to anemia in CKD by reducing the gastrointestinal absorption of iron. In addition, inflammation has been reported to partly account for erythropoietin hypo-responsiveness (29, 30). Therefore, this finding suggests that addressing some factors associated with both NPR and LPR may improve anemia in CKD.

There was a significant correlation between inflammatory markers and some atherogenic lipid components and ratios such as TG, HDL-C, TC: LDL-C, TG:HDL-C, and AIP. This finding is similar to reports of some previous studies (11, 25). The finding in this study may therefore suggest that increased risk of cardiovascular disease associated with inflammation may be partly mediated by its relationship with atherogenic lipid and atherosclerosis.

There are established non-pharmacological and pharmacological interventions that have been reported to reduce inflammation in CKD. The non-pharmacological intervention includes regular exercise, consumption of a high fiber diet, and omega-H3 fatty acids (8). Pharmacological intervention includes the use of statins which have been found to have non-pleiotropic actions such as atheromatous plaque stabilization, improvement of endothelial function, anti-thrombogenic effects, and antioxidant effects (31). These actions are potentially beneficial in the reduction of inflammation associated with cardiovascular risk. Adequate control of traditional cardiovascular risk factors has also been shown to reduce the level of inflammation in CKD (8).

The limitation of this study is that comparison was not made between NPR, LPR, and conventional inflammatory markers such as C-reactive protein and interleukins due to cost. The sample size of this study was relatively small; hence the findings cannot be generalized. However, the findings of this study have brought to the limelight the importance of these cheap and readily available inflammatory markers.

In conclusion, NLR and PLR were significantly higher in pre-dialysis CKD patients compared to controls without CKD. These inflammatory markers were significantly associated with hematocrit, eGFR, albumin, atherogenic lipid fractions, and ratios which are associated with cardiovascular disease. These readily available and cheap inflammatory markers should be routinely used in stratifying CKD patients to identify those with high cardiovascular risk. Proven non-pharmacological and pharmacological interventions should be promptly instituted in those with increased cardiovascular risk.

List of abbreviations

CKD: Chronic kidney disease
eGFR: Estimated glomerular filtration rate
NLR: Neutrophil-lymphocyte ratio
PLR: Platelet-lymphocyte ratio
AIP: Atherogenic index of plasma
TC: Total cholesterol
TG: Triglyceride
HDL-C: High-density lipoprotein-Cholesterol
LDL-C: Low-density lipoprotein-Cholesterol

Declarations

Ethical approval and consent to participate

Ethical approval was obtained from the Human Research and Ethical Committee of the University of Abuja Teaching Hospital. Informed consent was obtained from all participants in the study. Confidentiality of the provided information was ensured throughout the study.

Consent for publication

Availability of data and materials

The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests to declare.

Funding Statement

The authors are the sole funders of the research.

Authors' Contributions

MM and UI contributed to the conception, design and the acquisition of data of the work. MM, and AO contributed to the analysis and interpretation of data and to the writing of the manuscript.

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