

Original Article

Association between Seminal Plasma Creatine Kinase Activity and Sperm Quality Indices among Men Investigated for Infertility in Benin City, Nigeria

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HISTORY:

Received: 04-06-2026
Revised: 07-07-2026
Published: 12-07-2026

FUNDING

The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this study.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT:

Background: Numerous causes of male infertility have been well documented, but fewer studies have associated seminal plasma creatine kinase activity with abnormal sperm indices in men investigated for infertility.

Objective: To assess the association between seminal plasma creatine kinase activity and sperm quality indices among men investigated for infertility in Benin City, Nigeria, to elucidate its potential role as a biomarker of sperm function and male reproductive health.

Methods: Seminal fluid analysis was performed according to World Health Organization standards, and seminal plasma creatine kinase activity was assayed using a spectrophotometric technique in 75 infertile men (≥ 12 months of failed conception) as study participants and 50 fertile men (recent natural live birth) as controls.

Results: The mean volume (mL), sperm count ($\times 10^6/\text{mL}$), total motility (%), progressive motility (%), and viability (%) of infertile males were significantly lower ($P < 0.05$) when compared with the control group, while creatine kinase (IU/L) and abnormal morphology (%) were significantly higher in the infertile group when compared with the control group ($P = 0.001$). In infertile men, seminal plasma creatine kinase activity was significantly and inversely correlated with sperm count, total motility and viability, and positively correlated with abnormal morphology, but not with semen volume or progressive motility. The limitations of this study include a small sample size, its execution at a single center, and the lack of oxidative stress measurements.

Conclusion: The associations between seminal plasma Creatine Kinase activity and sperm quality indicators, apart from semen volume and progressive motility, suggest Creatine Kinase's potential as a biochemical marker for sperm dysfunction and male infertility.

Keywords: Male, Nigeria, Semen, Creatine Kinase, Infertility

Cite this article as: Asiriwa, I., Eweka, O.M., Emokpae, L.A., Obasuyi, G.E., Enaruna, N.O., Emokpae, M.A. (2026) Association between Seminal Plasma Creatine Kinase Activity and Sperm Quality Indices among Men Investigated for Infertility in Benin City, Nigeria. *Journal of Basic and Applied Research in Biomedicine*, 12(1): 23-27



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INTRODUCTION

There is an increasing prevalence of men with infertility cases; this increase could be resulting from a drastic decline in sperm quality and quantity over the years (Levine *et al.*, 2023). Studies have shown that there have been declines in male fertility globally, especially in low-income countries like Nigeria (Huang *et al.*, 2023). Infertility is the inability of a man or woman of reproductive age to achieve conception after 12 (twelve) months of uninterrupted and unprotected sexual copulation (Eisenberg *et al.*, 2023). Infertility can affect males and females or both at the same time, causing social-psychological and financial burden to the affected individuals (Kapoor *et al.*, 2025). Male infertility has been documented to contribute to about 20-43% of cases of infertility globally (Agarwal *et al.*, 2022), and this is more predominant in developing countries (Huang *et al.*, 2023). A report by Mann *et al.* (2020) shows that there has been a substantial decline in sperm quality, even though the causative factors have not been fully elucidated.

Routine semen analysis, which assesses volume, count, and motility, is considered the gold standard for diagnosing male infertility (Ngwu *et al.*, 2017; Agarwal *et al.*, 2021; WHO, 2021). However, it often does not uncover the underlying molecular or cellular defects (Magalhães *et al.*, 2021). Therefore, there is a pressing clinical necessity to incorporate additional metabolic markers, which are crucial for

understanding the pathophysiological mechanisms associated with abnormal semen parameters (Cox *et al.*, 2022).

Spermatogenesis requires a large amount of energy in the form of adenosine triphosphate (ATP); the source of this energy might be obtained from creatine kinase activity on creatine within the male reproductive tract (Emokpae *et al.*, 2022). Creatine kinase is essential for both the energy buffering required during sperm development and the high-energy demands of flagellar motility in mature spermatozoa. Creatine kinase, with different isoenzymes such as CK-BB, CK-MB, and CK-MM, has the same enzyme activity but is located in different tissues or organs of the body (Schlattner *et al.*, 2018), with CK-BB being highly abundant in seminal plasma.

Elevated CK activity could serve as a proxy for disrupted sperm metabolic-maturational status, which is often associated with decreased concentration, poor motility, diminished vitality, and abnormal morphology. The most compelling interpretation may not be that CK directly induces these seminal irregularities, but rather that increased CK levels may indicate a sperm population enriched with immature and functionally impaired cells.

Understanding these abnormalities may provide deeper insights into the pathophysiology of male infertility and improve the predictive value of fertility assessments. Therefore, this study aimed to assess the association between seminal plasma creatine kinase activity and sperm quality indices among men investigated for infertility in Benin City, Nigeria, to elucidate its

potential role as a biomarker of sperm function and male reproductive health.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study that involved randomly selected male partners of infertile couples attending a fertility clinic, while men with proven fertility served as control participants.

Study Site

Seminal fluid collections and analysis were performed in the Human Reproduction and Research Unit (HRRU) fertility clinic unit, while the analysis of seminal plasma creatine kinase activity was conducted at the chemical pathology laboratory. Both sites are located at the University of Benin Teaching Hospital (UBTH).

Sample Size

The minimum sample size was calculated using the prevalence rate of 5% in the targeted population (Okonofua, 2003)

$$n = Z^2 Pq/d^2$$

Where n = Sample size, Z = 1.96, the value corresponding to a 95% confidence level, P = Proportion in the target population estimated to have a particular characteristic, q = (1-p), and d = precision (margin of error) (5%)

$$n = (1.96)^2 \times 0.05 \times (1 - 0.05) / (0.05)^2 = 72.99$$

A total of 75 infertile men served as the study group, while 50 men with proven fertility served as the control group and were enrolled in this study. With a two-sided (α) level set at 0.05 and an unequal distribution of 75 cases relative to 50 controls, the study design achieves 80% statistical power to detect a Cohen's d effect size of 0.51 through a two-sample t-test.

Inclusion and Exclusion Criteria

Males of reproductive age who have been confirmed infertile (≥ 12 months of failed conception) served as study participants, and fertile men (recent natural live birth) served as controls, while those who are on antioxidant supplements and medication were excluded. Also, those with genital infection, varicocele, leukocytospermia, chronic illness, serious systemic diseases, sexually transmitted diseases, alcohol abuse, and smoking history were excluded.

Ethical Consideration

Ethical approval for this study was granted by the Ethics Review Committee of the Edo State Ministry of Health, Benin City, Nigeria (Ref. No. HA/737/25/D/07090762). Prior to sample collection, the nature and scope of the study were explained to all participants in their primary language, and written informed consent was obtained from each participant before enrolment.

Anthropometric and Demographic Measurements

Clinical and Anthropometric measurements regarding each participant's sex, age, weight, and height were obtained, and body mass index was calculated.

Body mass index (BMI): BMI = weight (kg)/height squared (m^2).

Structured questionnaires were administered to obtain the socio-demographic characteristics of the participants.

Sample Collection

Semen samples were obtained by masturbation after 3-5 days of sexual abstinence into clean, sterile, and leakproof universal sample containers that were kept at an ambient temperature of between 20°C and 37°C, ensuring that no sperm was lost. After seminal fluid analysis on the semen samples, they were spun at 3000rpm for 20minutes to obtain the seminal plasma. The seminal plasma was stored at -20°C before analysis.

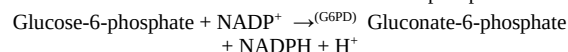
Seminal Fluid Analysis

Seminal fluid analysis (SFA) to examine volume, sperm count, total sperm motility, progressive motility, viability, and abnormal sperm morphology was done according to the World Health Organization standard (WHO, 2021).

Estimation of Creatine Kinase (CK) activity

Principle: In the total CK measurement, CK catalyzes creatine phosphate + ADP $\rightarrow$ creatine + ATP. The ATP produced is used by hexokinase to phosphorylate glucose, and glucose-6-phosphate dehydrogenase then converts glucose-6-phosphate, while reducing NADP⁺ to NADPH

The rate of formation of NADPH is monitored at 340 nm and is proportional to the activity of CK in the sample. These reactions occur in the presence of N-acetyl-L-cysteine (NAC) which is present as an enzyme reactivator. The increase in NADPH is read spectrophotometrically at 340 nm, and that signal is proportional to CK activity in the sample.



The assay was done using the Creatine kinase kit following the manufacturer's instructions (Abbott Diagnostics, ABBOTT Max-Planck-Ring 2, 65205 Wiesbaden, Germany).

Data analysis

Data generated were analyzed using Statistical Package for the Social Sciences software (version 20.0, IBM SPSS, Armonk, NY, USA). Comparison between means was done using the independent-samples t-test (unequal variances) and analysis of variance (ANOVA) for creatine kinase across BMI categories, while Chi-square was used for educational qualification and occupation, and Fisher's exact test for BMI categories because of small expected counts. Pearson correlation coefficient was used to determine the association between creatine kinase and sperm quality indices. The level of significance was set at $P < 0.05$.

RESULTS

Table 1: Demographic Characteristics of Study Participants (values in parentheses are formatted as n (%)).

Variables	Infertile Men N=75 (%)	Fertile Men N=50 (%)	F-Value/ χ^2	P-Value
Mean Age (Years)	40.32 $\pm$ 1.51	41.20 $\pm$ 1.20	0.46	0.65
25-34	19(25.3)	4(8.0)	6.56	0.038
35-44	38(50.7)	28(56.0)		
45-Above	18(24.0)	18(36.0)		
Educational Qualification				
Primary	18(24.0)	10(20.0)	1.25	0.54
Secondary	41(54.7)	25(50.0)		
Tertiary	16(21.3)	15(30.0)		
Occupation				
Civil Servant	30(40.0)	8(16)	8.2	0.004
Business	45(60.0)	42(84.0)		
BMI				
Underweight	02(2.7)	1(2.0)	–	0.56
Normal weight	68(90.7)	48(96.0)		
Overweight	05(6.7)	1(2.0)		

BMI: Body mass index, $P < 0.05$ was considered statistically significant while $P > 0.05$ was considered not statistically significant.

Table 2: Comparison of the mean levels of Creatine Kinase and Sperm Indices between males investigated for infertility and Control group using Student-t-test:

Parameters	Infertile males N=75	Control N=50	t-value	P-Value
Creatine Kinase*	756.45 $\pm$ 23.70 (95%CI.710, 802.9)	412.60 $\pm$ 19.56 (95%CI.374.26,450.9)	11.2	0.001
Volume*	2.20 $\pm$ 0.02 (95%CI.2.16, 2.24)	(2.75 $\pm$ 0.06) (95%CI.2.63, 2.87)	-8.7	<0.001
Sperm Count	18.30 $\pm$ 1.04 (95%CI.16.26, 20.43)	38.18 $\pm$ 2.60 (95%CI.33.1, 43.28)	-7.1	0.001
Total motility*	14.30 $\pm$ 3.10 (95%CI.8.22, 20.38)	42.20 $\pm$ 2.40 (95%CI.37.5,46.92)	-7.1	0.001
P. motility*	11.60 $\pm$ 2.02 (95%CI.7.64, 15.56)	34.22 $\pm$ 2.60 (95%CI.29.12, 39.32)	-6.9	0.001
Viability*	18.32 $\pm$ 0.20 (95%CI.17.92, 18.72)	59.18 $\pm$ 2.50 (95%CI.54.3, 64.1)	-16.0	0.001
A. Morphology*	27.89 $\pm$ 1.50 (95%CI.24.95,30.83)	7.30 $\pm$ 2.50 (95%CI.2.40, 12.2)	7.1	0.001

CK=Creatine kinase activity; P. motility= Progressive motility; A. Morphology= Abnormal morphology. Data are expressed as mean $\pm$ Standard Error of Mean; $P < 0.05$ was considered statistically significant, while $P > 0.05$ was considered not statistically significant, and 95% confidence interval in parentheses. * denotes IU/L, * denotes mL, +denotes $\times 10^6/\text{mL}$, # denotes percentage.

This study is made up of a total of 125 participants, comprising of seventy-five (75) study participants and fifty (50) control participants. Table 1 represents the demographic data of study participants. The mean $\pm$ SEM age of men investigated for infertility was not statistically different ($P > 0.05$) from that of the control participants. When the ages were stratified, a significant difference was observed between the two groups ($P = 0.038$). The educational attainment of the study participants was not significantly different from that of the controls ($P = 0.54$). All study participants were either civil servants or businessmen, and the difference between the groups was statistically significant ($P = 0.004$). Similarly, the majority of the study group was within a healthy weight range classification, with only 02/75 (2.7 %), 68/75 (90.7 %), and 05/75 (6.7 %) being underweight, a normal-range body weight, and overweight, respectively.

Table 2 indicates that creatine kinase activity (IU/L) in the seminal plasma of study participants was markedly raised ($P = 0.001$) when compared with the controls. The semen volume (mL), sperm count ($\times 10^6/\text{mL}$), total motility (%), progressive motility (%), and viability (%) were markedly lower in study participants when compared with the control group. Conversely, the abnormal morphology (%) was markedly higher in study participants than in the control group.

Table 3 reports the mean seminal plasma creatine kinase activity across the BMI strata of study participants. Although CK activity increased with higher BMI categories, the difference in mean levels was not statistically significant.

Table 4 shows the relationship between creatine kinase activity and sperm quality indices among the study participants. All sperm quality indices except semen volume and progressive motility were significantly and negatively correlated with creatine kinase activity, while abnormal sperm morphology correlated positively with seminal plasma creatine kinase activity ($P < 0.05$).

Table 3: Seminal Plasma Creatine Kinase Activity across BMI categories of study Participants.

Body Mass Index	Infertile Men		Controls	
	N	Creatine kinase	N	Creatine kinase
Under weight	02	748.50 $\pm$ 6.20 95%CI. 736.35, 760.65	01	398
Normal weight	68	756.18 $\pm$ 10.20 95%CI. 736.18, 776.17	48	420.7 $\pm$ 18.20 95%CI. 385.02, 456.37
Overweight	05	762.48 $\pm$ 9.80 95%CI. 743.27, 781.68	01	419
		F=2.12; P>0.05		

Data are expressed as mean $\pm$ Standard Error of Mean, and 95% confidence interval in parentheses.

Table 4: Relationship between Creatine Kinase and Sperm Indices among Infertile Male Participants using Pearson correlation coefficient.

Correlation	r	P
Volume/Creatine kinase activity	-0.049	0.584
Sperm count/Creatine kinase activity	-0.582	0.001
Total motility/ Creatine kinase activity	-0.690	0.001
Progressive motility/ Creatine kinase activity	-0.222	0.056
Viability/Creatine kinase activity	-0.488	0.001
Abnormal morphology/Creatine kinase activity	0.338	0.003

$P < 0.05$ was considered statistically significant, while $P > 0.05$ was considered not statistically significant.

DISCUSSION

This study explored the association between seminal plasma creatine kinase (CK) activity and semen quality parameters in men undergoing infertility evaluation in Benin City, Nigeria. The results revealed that infertile men displayed significantly lower measures in semen sperm count, total motility, progressive motility, and sperm viability compared to their fertile counterparts. Conversely, the percentage of abnormal sperm morphology was markedly elevated in the infertile group. Additionally, seminal plasma CK activity showed significant

negative correlations with sperm count, total motility, and viability, and a significant positive correlation with abnormal sperm morphology. However, semen volume was significantly lower in infertile men (Table 2), but it did not directly correlate with the levels of CK activity (Table 4).

The increasing rate of male infertility is alarming globally, especially in developing countries like Western sub-Saharan Africa, including Nigeria, Eastern Europe, and East Asia (Huang et al., 2023). Adequate attention has to be channeled into reducing the rate of infertility among men of reproductive age, hence the need to perform this study. The study aimed to assess the relationship between seminal plasma creatine kinase activity and seminal indices, and to establish the effects of abnormal seminal CK activity on seminal indices of men investigated for infertility.

The mean ages of the study participants and control group were similar ($P = 0.65$), although the age-group distribution differed ($P = 0.038$); the majority of participants in both groups were between 35 and 44 years. This finding was similar to a previous study conducted to assess the effect of age on male fertility (Halvaei et al., 2020). It was reported that paternal age can cause a reduction in seminal indices through some cellular and physiological changes, ranging from a decrease in germ cells and androgen levels, a reduction in the ability to cause cellular repairs, and an increase in tissue damage and systemic disease, and also due to anatomic changes such as narrowing of the seminiferous tubule and vascular insufficiency (Halvaei et al., 2020).

The significantly reduced semen volume observed among infertile men points to a potential impairment in the secretory functions of accessory sex glands, such as the seminal vesicles and prostate gland. Semen volume plays a crucial role in facilitating sperm transport, survival, and the potential for fertilization. Reduced ejaculate volume can hinder effective sperm delivery to the female reproductive tract and may be indicative of underlying dysfunction within the reproductive system. This finding corroborates earlier research linking infertility and abnormal seminal characteristics with decreased semen volume (Barone et al., 2026). It should be noted that accessory gland secretory output (volume) seems to be a separate pathological feature of infertility in this cohort, independent of the cytoplasmic retention/metabolic pathways reflected by seminal plasma CK.

The notable drop in sperm count among infertile participants underscores disruptions in spermatogenesis and potential testicular dysfunction. Sperm concentration remains one of the key determinants in assessing male fertility potential. Contributing factors to reduced sperm production may include oxidative stress, hormonal imbalances, environmental toxins, infections, genetic disorders, or abnormalities in germ cell maturation. The low sperm counts observed align with prior studies highlighting the prevalence of oligozoospermia and significantly diminished sperm production among infertile men (Sciorio et al., 2024; Rodak et al., 2025).

Furthermore, the pronounced reduction in total motility, progressive motility, and sperm viability among infertile individuals reflects a compromise in functional sperm integrity. Sperm motility relies heavily on adequate ATP synthesis and efficient energy distribution to the flagellum, with progressive motility being critical for navigating through the female reproductive system and achieving fertilization. The decrease in sperm viability suggests impaired cellular membrane stability and increased damage, both of which likely contribute to diminished fertilization capacity. Collectively, these abnormalities highlight key factors underlying male infertility and their potential impact on reproductive outcomes (Kaltsas, 2023).

The higher incidence of abnormal sperm morphology among infertile men reinforces the notion of defective spermatogenesis and impaired sperm maturation. These abnormalities in sperm structure—which commonly affect the head, midpiece, or tail—can hinder motility, compromise DNA integrity, disrupt capacitation, and impair fertilization. Elevated rates of abnormal

morphology consistently correlate with poor reproductive outcomes and diminished pregnancy success (Pelzman and Sandlow, 2024).

A key observation from this study is the significant negative relationship between seminal plasma creatine kinase (CK) activity and critical semen quality parameters, including sperm count, total motility, and viability. This suggests that increased CK activity corresponds to declining sperm quality. CK plays a vital role in cellular energy metabolism by facilitating the reversible conversion of creatine and ATP into phosphocreatine and ADP. In mature sperm cells, CK supports energy buffering and transport mechanisms essential for mobility and other energy-dependent functions (Brewster, 2018; Bonilla *et al.*, 2021).

Nonetheless, heightened CK activity in seminal plasma is often linked to the presence of immature spermatozoa and disrupted spermiogenesis. During healthy sperm maturation, excess cytoplasm is expelled from developing sperm cells; failure to remove residual cytoplasm leads to increased CK activity, as the enzyme accumulates within the cytoplasmic compartment of immature germ cells. Elevated seminal CK activity may therefore indicate incomplete sperm maturation and a greater prevalence of immature sperm in the ejaculate, sperm that typically exhibit reduced motility, decreased viability, and compromised fertilization potential (Nasrallah *et al.*, 2020; Babatunde and Emokpae, 2022; Emokpae *et al.*, 2022). The failure to eliminate residual cytoplasm is primarily a defect of spermiogenesis (within the seminiferous tubules of the testes), though subsequent membrane stability changes occur during transit through the epididymis.

The observed negative correlation between CK activity and sperm count implies that higher CK levels may signal testicular dysfunction and compromised spermatogenic capacity. In cases of defective spermatogenesis, there is often an increased release of immature spermatozoa, resulting in higher CK activity and lower sperm production. Similarly, the inverse relationship between CK activity and total motility underscore how metabolic inefficiency and immaturity can impair sperm movement. Given that motility demands substantial ATP expenditure, disruptions in energy metabolism likely contribute to reduced flagellar functionality.

The observed inverse relationship between CK activity and sperm viability can likely be attributed to heightened oxidative stress linked to the retention of cytoplasm as reported in the literature (Babatunde and Emokpae, 2022; Emokpae *et al.*, 2022). Residual cytoplasm harbors elevated concentrations of enzymes that contribute to reactive oxygen species (ROS) production, which, when excessive, can lead to lipid peroxidation of sperm membranes, mitochondrial impairment, and apoptotic alterations—ultimately diminishing sperm survival and viability. This mechanism may further elucidate the reduced motility found among infertile subjects.

On the other hand, the notable positive correlation between CK activity and abnormal sperm morphology reinforces the idea that increased seminal CK activity indicates defective sperm maturation. Morphological abnormalities commonly stem from disruptions during spermatogenesis and spermiogenesis, processes integral to cytoplasmic elimination and cellular remodeling. As such, elevated CK activity might serve as a biochemical marker signaling irregular sperm development and structural anomalies. Similarly, higher seminal CK activity has been associated with poorer spermogram parameters in men with infertility (Zequiraj *et al.*, 2019).

These insights suggest that seminal plasma CK activity is intricately tied to sperm quality and could play a complementary role in the underlying mechanisms of male infertility. Elevated CK levels appear to reflect impaired maturation, dysregulated energy metabolism, oxidative stress, and flawed spermatogenesis—all factors that collectively undermine sperm count, motility, viability, and normal morphology. The correlations identified in this research highlight seminal plasma CK as a potential supplementary biomarker for assessing male reproductive health beyond standard semen analysis.

This research is not without limitations. Firstly, the relatively small sample size may have diminished the statistical power to identify subtle relationships among the studied variables. Secondly, the study was conducted at a single center, which may limit the external validity and generalizability of the findings. Thirdly, oxidative stress biomarkers were not evaluated, despite the recognized role of oxidative stress in the pathophysiology of numerous endocrine, metabolic, and reproductive disorders. As a result, the study may be unable to ascertain whether oxidative stress mediated the observed associations, nor could it assess the balance between oxidant production and antioxidant defense. Finally, the groups differed significantly in occupation, so residual confounding cannot be excluded. However, these limitations do not undermine the importance of the findings; they highlight the necessity for future research involving larger, multicenter cohorts and the incorporation of comprehensive oxidative stress and antioxidant biomarkers.

CONCLUSION

Men with infertility showed poorer seminal profiles and higher rates of sperm morphological abnormalities compared to fertile men. The negative associations between seminal plasma CK activity and sperm quality indicators, along with its positive correlation with abnormal morphology, suggest CK's potential as a biochemical marker for sperm dysfunction and male infertility. There was no significant correlation of creatine kinase activity with semen volume or progressive motility. Further investigation is suggested to determine whether seminal plasma creatine kinase activity meets the essential criteria for a clinically useful biomarker, namely, analytical validity, clinical validity, and clinical utility. If validated through large-scale multicenter studies and standardized laboratory protocols, seminal plasma creatine kinase activity has the potential to become a valuable adjunct to conventional semen analysis, improving the diagnosis, prognostic assessment, therapeutic monitoring, and management of male infertility.

ETHICS APPROVAL

Ethical approval was obtained from the Ethics Review Committee of the Edo State Ministry of Health, Benin City, Nigeria (Ref. No. HA/737/25/D/07090762). Written informed consent was obtained from all individual participants included in the study prior to sample collection.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

The authors acknowledge that AI-assisted technologies were sparingly used in the preparation of the initial draft of this manuscript. Specifically, generative AI tools (ChatGPT) were employed to support language refinement and grammar correction. All content was critically reviewed, edited, and approved by the authors to ensure accuracy, originality, and alignment with academic standards. No AI tools were used to generate data, interpret results, or replace human intellectual contribution.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this study.

FUNDING

The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

IA, OME, LAE, MAE, NOE conceived and designed the study, supervised the experiments, and data collection. IA, OME, LAE, and GEO performed the laboratory experiments, analyzed the data, and drafted the manuscript. IA, GEO, OME, LAE, NOE and MAE. conducted the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

ACKNOWLEDGMENTS

We acknowledge the contributions of the Clinicians, Nurses, and Medical laboratory scientists of the University of Benin Teaching Hospital and staff of the Department of Medical Laboratory Science, University of Benin, Benin City, toward the completion of the study.

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