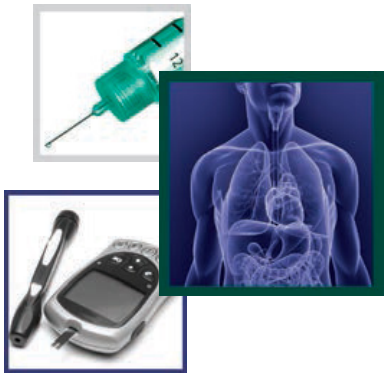
RESEARCH ARTICLE

Diabetes Management



Serum Gamma-Glutamyl Transferase as a risk biomarker in predicting cardiovascular disease among diabetics: A cross-sectional descriptive study in Ghana

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ABSTRACT

Aim: This study evaluated the use of serum Gamma-Glutamyl Transferase (GGT) as a risk biomarker in the development of cardiovascular diseases among Type 2 Diabetes Mellitus (T2DM) individuals. Method: This was a cross-sectional study one conducted among 185 diabetics at Effia-Nkwanta Regional Hospital. Questionnaires were administered regarding socio-demographic characteristics and exclusion of individuals with confounding conditions. Measurement of anthropometric indices, blood sample collection and estimation serum GGT and lipid profile was done for qualified participants. Data was entered and analysed using Grpahpad Prism version 6. Results: A total of 185 participants were enrolled in the study. The mean age of the participants was 57.9 ± 9.9 years with majority of them between 50-60 years (36%). There were more females (77%) than males (23%). A significant difference in GGT levels was observed for duration of diabetes among the participants (p=0.0286). Indicators of central obesity were higher as stratified by the indices, Weight-to Height Ratio (WHtR) (81%), and Weight-to-Hip (WHR) (75%). Positive association between GGT levels and body mass index (BMI), waist circumference (WC), WHR, Body Adiposity (BAI), coronary risk (CR), conicity (CI), total cholesterol (TC), Triglyceride, very low density lipoprotein (VLDL) and Glucose concentrations were observed. Total cholesterol (aOR=2.35, p<0.0001), TG (aOR=3.01, p=0.004), and LDL-C (aOR=2.05, p<0.001) were significant associated with increased risk of developing CVD, however, significantly reduced risk was observed for HDL-C after controlling for cofounders. Receiver operating characteristics (ROC) curve analysis of GGT in predicting its accuracy in diagnosing risk of coronary events showed that area under curve AUC was 75.81% for a 37.90U/L serum GGT cut-off value with 60% sensitivity and 90% specificity. Conclusion: GGT demonstrated a high accuracy, good sensitivity and a high specificity in predicting coronary risk among the participants, together with showing good relationship with established risk markers.

Introduction

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels, and most often than not, cardiovascular diseases have been linked to increased oxidative stress and dyslipidemia [1]. In both types of diabetes, it has been proven that there is increase in the generation of reactive oxygen

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KEYWORDS

- gamma glutamyl transferase
- risk
- cardiovascular disease
- diabetes mellitus
- anthropometric indices
- lipid profile

species, causing oxidative stress [2], leading to incidence of cardiovascular diseases and the risk of cardiovascular disease induced mortality [3]. With a limited pool of glutathione as a result of the increased oxidative stress in diabetic subjects, serum Gamma Glutamyl transferase (GGT), a plasma membrane enzyme whose major function is to recycle extracellular glutathione to provide precursors for intracellular glutathione formation increases [4]. Though aiding in salvaging the oxidative status of the body, its activity tends to lead to an unintended oxidation of low-density lipoprotein (LDL) cholesterol, felt to participate in atheroma formation in the development of atherosclerosis, a prominent cardiovascular disease [4]. Cardiovascular diseases pose a threat to human health with increasing morbidity and mortality rate. According to the 2016 Global report on diabetes mellitus (DM) by WHO, diabetes caused 1.5 million deaths in 2012 [5]. In Accra, Ghana, CVD was the leading cause of death in 1991 and 2001 [6]. Diabetes acts as an independent risk factor for several forms of CVD. Globally, high blood glucose causes about 7% of deaths among men aged 20–69 and 8% among women aged 20–69, most of this mortality resulting from the development of cardiovascular diseases in these individuals [7]. These considerations have convinced the Scientific Advisory and Coordinating Committee of the American Heart Association (AHA) that diabetes mellitus deserves to be designated a major risk factor for CVD [8]. In addition to the conventional risk prediction algorithms and upcoming prediction markers such as the Framingham Heart Risk score, geared at reducing the burden of cardiovascular disease development through early diagnosis, GGT has emerged as an authentic and accurate biomarker of cardiovascular diseases [9]. Early identification of these risk factors are much needed to accelerate disease prevention and morbidity improvement [10]. To our knowledge no study has been conducted to elucidate the role of GGT as a risk biomarker for cardiovascular among diabetics in a Ghana population. Therefore investigating of the role of GGT in the mechanism of cardiac diseases will thus be helpful in developing preventive strategies and treatment methods against cardiovascular diseases development in diabetics. A study in this regard will thus contribute to providing more information regarding the use of GGT as a diagnostic predictive tool in assessing cardiovascular disease development in diabetes mellitus patients. It will serve as a baseline for further studies to improve upon the existing store of knowledge in order to improve upon the quality of life among individuals.

Materials and Methods

Study design and setting

The study was a cross-sectional study among a representative sample of diabetics visiting the Effia-Nkwanta Regional Hospital in the Sekondi-Takoradi Metropolis of Ghana, with the use of structured questionnaire on interview basis as well as direct physical measurements and biochemical analysis of obtained samples. Effia-Nkwanta Regional Hospital is in the Western region of Ghana, and serves as the main referral centre for all medical conditions that require specialist attention. It is about 10 kilometres from Takoradi the regional capital. The hospital can be found on longitude 4.9239°N and latitude 1.7446°W on the globe.

Study population

The study population comprised of individuals with DM visiting the Out Patient Department of the hospital. A total of one hundred and eighty-five (185) participants were recruited using a simple random sampling technique. In order to determine the required sample size, the formula $n=Z^2PQ/d^2$ was used, where, Z=1.96, P=prevalence of diabetes which was 4.8% [11] and d= margin of error i.e. 0.05. Thus, the calculated sample size was n=70. With the minimum number to be enrolled being 70, we recruited 185 individuals in order to increase statistical power in this study.

Inclusion criteria

The target population for the study was both individuals recently or previously diagnosed of DM as at the time of the study without respect to either gender or age.

Exclusion criteria

Exclusion criteria included individuals with hepatitis and other hepatic disorders, cancers, alcohol consumers, Acquired Immune Deficiency Syndrome (AIDS), cytomegalovirus infections, smokers, individuals with autoimmune diseases and those on medications such as carbamazepine, barbiturates and phenytoin, and immune-compromised patients.

■ Data collection techniques and tools

The data collection was conducted in the steps outlined: Step 1 was used to capture information related to conditions that in themselves affect the serum GGT levels hence interfering with obtaining accurate and reliable results. This was achieved through the administration of questionnaires. Step 2 was used to capture information on weight, height, hip circumference and waist circumference. This was carried out using a locally purchased standard weighing scale for the weight of consented participants and a measuring tape used to measure the height, hip circumference and wrist circumference. Step 3 involved taking of blood samples from qualified respondents while Step 4 included sample preparation and biochemical analysis of the blood samples obtained to assay for the levels of parameters such as the lipid panel of cholesterols, triglycerides and serum GGT using the Selectra Pro S Biochemistry Auto-Analyzer (ELITechGorup Clinical Systems, Germany).

■ Ethical consideration

Ethical clearance (CHRPE/AP/137/17) for the study was obtained from the Committee on Human Research, Publication and Ethics (CHRPE), in KNUST School of Medical Sciences (SMS), Kumasi, Ghana. Approval for conduct of the study was also obtained from the administration of Effia-Nkwanta Regional Hospital. The aims and the processes of the research were fully explained to the participants and their informed consent obtained for participation.

■ Data handling and analysis

Descriptive statistics described frequency and means. All continuous variables were analysed based on the distribution of the variables; non-parametric data were expressed as medians and data with normal distribution were expressed as means. Student's t test and Man Whitney U test were used to test for differences in means and median respectively. Linear regression analysis was used to determine the relation between GGT and lipid parameters Receiver Operator Curve (ROC) was employed to determine the accuracy and cut-off point of GGT in predicting cardiovascular disease. GraphPad Prism version 6.00 and XLSTAT 2015, 4.01 for windows were used for statistical analysis where appropriate (GraphPad software, San Diego California USA).

Results

The mean age of the participants was 57.9 ± 9.9 years with a majority of the age group between 50-60 years (36%). There were more females (77%) than males (23%). The largest percentages of the participants were married (70%), urban dwellers (66%) and had not had any formal education (35%). Only 5% were on injection of insulin as a form of treatment while 95% were on Metformin. Considering the duration of diabetes of the participants recruited in the study, the median, inter-quartile range was 7(4-10) years with majority being less than 5 years (40%). **(TABLE 1)** After assessing selected variables for progressive linear increment or decline from the first through to the fourth quartile of GGT using linear contrast analysis, a significant additive incremental linear relationship was observed for CR and glucose with increasing quartile levels of GGT for coronary risk and glucose concentration but decreasing quartile levels for age. In the case of quartile cluster distribution for anthropometric indices, significant additive linear relationship was observed for WC (p value=0.009), WHtR (p value=0.018) and VAI (p value=0.034). In the case of quartile cluster distribution for lipid profile, significant additive linear relationship was observed for Triglyceride (p value=0.031), VLDL Cholesterol (p value=0.031) and Coronary risk (p value=0.006 **(TABLE 2)**. Multiple linear regression analysis was used to operationalize anthropometric indices and biochemical parameters with GGT being dependable variables. The predictor variables were the anthropometric indices and biochemical parameters. Multivariate analysis indicated significant model fit for the data (F=0.372 and p-value=0.000). The amount of variance in the GGT levels that is explained by the predictors is 37.2% (R2=0.372) with glucose levels being the strongest predictor of GGT levels (β=8.002; p<0.0001). A negative beta coefficient indicates a negative association between HC, WHtR, VAI, AVI, LDL-C and GGT levels. All the other parameters were not statistically significant associated with GGT levels **(TABLE 3)**. As shown in (**FIGURE 1)**, AUC was 75.81 (65.40-86.22) with significant asymptomatic p-value (<0.0001). Using a cut-off value of 37.90, GGT had a sensitivity of 60.00 (42.28-75.37) and specificity of 90.00 (80.39-95.28) with negative predictive value of 84.00% and positive predictive value 72.00%. As shown in **Table 4**, after controlling for age, gender, treatment options and duration of disease,

Table 1: General characteristics of study participants JHS and SHS are Junior High School and Senior High School respectively. Data is presented as figure with percentage in parenthesis, mean ± SD (standard deviation). IQR is Inter Quartile range and p is significant at 0.05. GGT levels are recorded as median (Inter-Quartile Range).

Variable	Frequency (n)	Percentages
Age (years)(mean ± SD)	57.9 ± 9.9	
Age Group (years)		
30-40	13	7.0%
41-50	26	14.1%
51-60	67	36.2%
61-70	57	30.8%
≥71	22	11.9%
Gender		
Male	42	22.7%
Female	143	77.3%
Marital Status		
Married	129	69.6%
Single	4	2.2
Divorced	26	14.1%
Widowed	26	14.1%
Educational Level		
Illiterate	65	35.1%
JHS	54	29.1%
SHS	52	28.1%
Tertiary	14	7.7%
Area of Residence **Rural** **Urban** **P value**	 63 122	 34.1% 65.9%
Treatment Type		
Metformin	176	95.1%
Injection	9	4.9%
Duration of Diabetes(Median/IQR)		
≤5	74	40.0%
6-10	69	37.3%
11-15	33	17.8%
≥16	9	4.9%

TC (aOR=2.35, p<0.0001), TG (OR=3.01, p=0.004), and LDL-C (OR=2.05, p<0.001) were significant associated with increased risk of developing CVD, however, significantly reduced risk was observed for HDL-C **(TABLE 4)**.

Discussion

Although GGT has been thought of as a diagnostic tool for hepatobiliary disorders and alcohol abuse [12], several studies have shown a strong association between serum GGT concentrations and many cardiovascular disease risk factors or components [13-15]. This study evaluated the levels of GGT in predicting the risk of cardiovascular diseases, specifically coronary risk events (a major example being atherosclerosis), among diabetes mellitus individuals at Effia Nkwanta Regional Hospital. The results of the study found that 95% of the participants were on Metformin as a form of therapy and 5% were on insulin. In this study, the levels of GGT showed no statistical difference among the age groups, gender and educational level of participants in the study. These findings are inconsistent with findings from studies by Lee et al., [16] in Korea and Ford et al., [17] in United States (US), where they observed significant difference in GGT levels among the age groups of diabetics. Sabanayagam et al., C Sabanayagam, A Shankar, J Li, C Pollard and A Ducatman [18] also observed a significant difference in GGT levels among the level of education and gender of diabetics in their study carried out among US adults. This observed inconsistency may be due to the adherence of study participants to lifestyle modelling (irrespective of their age group, sex and educational level), geared towards decreasing the

Table 2: Linear contrast analysis of quartile cluster distribution of GGT stratified by age, anthropometric and biochemical parameters. BMI= Body Adiposity Index, WC= Waist Circumference, HC= Hip Circumference, WHR= Waist-to-Hip Ratio, WHtR= Waist-to-Height Ratio, BAI= Body Adiposity Index, VAI= Visceral Adiposity Index, CR= Coronary Risk, CI= Conicity Index, AVI= Abdominal Volume Index. P is significant at 0.05.

		GGT Quartiles			
Variables	**Q1(<21.03)**	**Q2(21.03-27.2)**	**Q3(27.2-38.88)**	**Q4(>38.88)**	**p-trend**
Age	60.2 ± 8.7	58.2 ± 11.4	57.6 ± 7.8	55.6 ± 11.2	0.113
BMI	25.66 ± 3.8	29.34 ± 5.7	28.8 ± 5.0	28.9 ± 9.0	0.107
WC (cm)	92.9 ± 11.1	104.3 ± 9.2	100.3 ± 10.9	103.6 ± 15.1	0.009
HC (cm)	102.6 ± 16.9	112.0 ± 9.1	105.0 ± 9.5	110.4 ± 19.7	0.209
WHR	0.92 ± 0.10	0.93 ± 0.06	0.95 ± 0.05	0.94 ± 0.08	0.157
WHtR	0.58 ± 0.07	0.65 ± 0.06	0.63 ± 0.08	0.64 ± 0.09	0.018
BAI	32.2 ± 8.4	37.2 ± 6.6	34.0 ± 6.2	35.9 ± 11.5	0.299
VAI	3.3 ± 1.5	3.8 ± 2.4	3.2 ± 1.5	4.7 ± 2.5	0.034
CR	4.8 ± 1.3	4.9 ± 1.6	5.0 ± 1.6	6.5 ± 3.1	0.006
CI	1.33 ± 0.14	1.41 ± 0.11	1.36 ± 0.11	1.43 ± 0.26	0.089
AVI	17.7 ± 4.2	22.0 ± 3.9	20.4 ± 4.4	22.0 ± 6.5	0.011
Glucose (mmol/L)	7.2 ± 1.4	8.0 ± 1.8	8.5 ± 1.8	11.9 ± 3.8	<0.0001
TC (mmol/L)	5.28 ± 1.31	5.27 ± 1.17	5.71 ± 1.25	5.90 ± 1.76	0.066
TG (mmol/L)	1.77 ± 0.64	1.94 ± 0.67	1.92 ± 0.50	2.21 ± 0.79	0.031
LDLC(mmol/L)	3.3 ± 1.1	3.2 ± 1.1	3.6 ± 1.3	3.9 ± 1.5	0.058
VLDL-C (mmol/L)	0.81 ± 0.29	0.88 ± 0.30	0.87 ± 0.23	1.00 ± 0.36	0.031
HDL-C(mmol/L)	1.16 ± 0.35	1.18 ± 0.43	1.22 ± 0.34	1.03 ± 0.37	0.289

Table 3: Multiple linear analysis between GGT and anthropometrics and biochemical parameters. R^2 =0.372, F =3.32 and p< 0.0001, BMI= Body Adiposity Index, WC= Waist Circumference, HC= Hip Circumference, WHR= Waist-to-Hip Ratio, WHtR= Waist-to-Height Ratio, BAI= Body Adiposity Index, VAI= Visceral Adiposity Index, CR= Coronary Risk, CI= Conicity Index, AVI= Abdominal Volume Index.

	GGT Levels		
Variable	**B-coefficient**	**Standard error**	**P-value**
BMI ((Kg/m²)	0.067	2.30	0.977
WC (cm)	11.78	9.086	0.198
HC (cm)	-6.179	5.702	0.282
WHR	52.046	244.53	0.832
WHtR	-16.90	13.1	0.201
BAI	13.68	10.70	0.205
VAI	-3.480	5.454	0.525
CR	1.519	4.794	0.752
CI	32.24	62.738	0.609
AVI	-4.202	8.418	0.619
Glucose (mmol/L)	8.002	1.597	<0.0001
TC (mmol/L)	5.387	6.876	0.436
TG (mmol/L)	7.915	11.107	0.478
LDL-C(mmol/L)	-10.282	5.748	0.077
VLDL-C(mmol/L)	24.65	14.81	0.099
HDL-C(mmol/L)	1.201	20.917	0.954

risk of complications associated with the disease, particularly increase in oxidative stress that will tend to trigger the significant increase in GGT levels [19]. The levels of GGT on the other hand showed a statistical significance with respect to participants' duration of diabetes. Studies by Al-Dahhan [20] in Iraq and Zoppini et al. [21] among the Italian population in the Verona

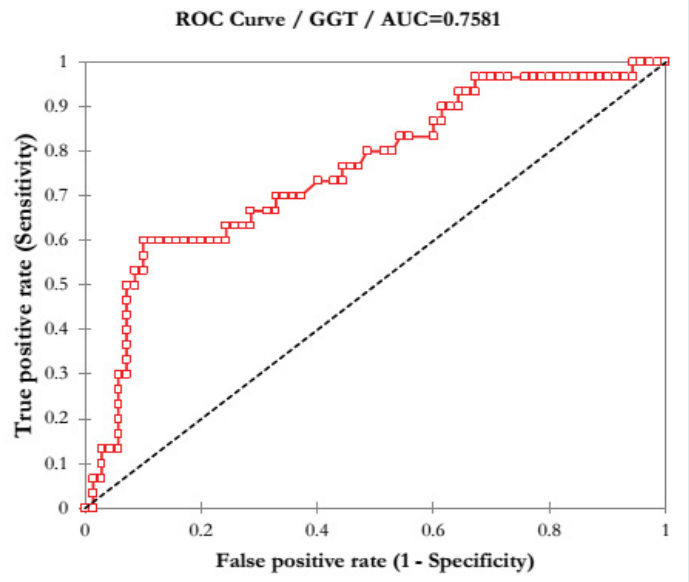

Figure 1: Receiver operating characteristic (ROC) curve for depicting the accuracy of GGT in diagnosing coronary risk.

Table 4: Multiple logistic regression of anthropometric indices and biochemical parameters predicting risk of coronary events controlling for age, gender, treatment options an duration of disease. AOR=adjusted Odds Ratio, CI=Confidence Interval BMI= Body Adiposity Index, WC= Waist Circumference, HC= Hip Circumference, WHR= Waist-to-Hip Ratio, WHtR= Waist-to-Height Ratio, BAI= Body Adiposity Index, VAI= Visceral Adiposity Index, CR= Coronary Risk, CI= Conicity Index, AVI= Abdominal Volume Index, p<0.05 is statistically significant.

Variables	AOR (95%CI)	p-value
WHR	0.31(0.001-7.60)	0.673
WHtR	2.15(0.01-41.7)	0.775
BMI (Kg/m^2)	0.96(0.87-1.08)	0.311
BAI	1.03(0.92-1.10)	0.343
AVI	1.01(0.92-1.10)	0.932
CI	3.63(0.33-13.2)	0.215
Glucose (mmol/L)	1.07(0.88-1.31)	0.504
GGT (mmol/L)	1.82(0.99-2.01)	0.115
TC (mmol/L)	2.35(1.54-3.61)	<0.001
TG ((mmol/L)	3.01(1.43-6.35)	0.004
LDL-C (mmol/L)	2.05(1.38-3.03)	<0.001
VLDL-C (mmol/L)	1.45(1.22-5.91)	0.051
HDL-C (mmol/L)	0.12(0.002-0.14)	<0.0001

study reported similar findings that GGT levels strongly correlate with the duration of diabetes. This could be attributed to the fact that elevated GGT is strongly associated with obesity and excess deposition of fat in the liver and this is thought to cause hepatic insulin resistance and to contribute to the development of systemic insulin resistance and hyperinsulinemia [22]. Previous studies have suggested that WC is a good indicator for predicting the risk of cardiovascular disease [23,24]. A strong positive relation was observed between GGT and WC in this study which strongly suggests the predictive value of GGT in assessing cardiovascular risk. Moreover, a positive association between GGT levels and BMI, Total Cholesterol, Triglyceride and Glucose

concentrations were observed. This is consistent with studies by Lee et al, the Framingham heart study by Lee et al., [25], Fonseca et al., [26] in the US and Ruttmann et al., [27] in Austria, where they found GGT to be positively associated with significant risk factors for cardiovascular disease including BMI, serum triglycerides, total cholesterol, systolic and diastolic blood pressure, and glucose. These factors have been known to show strong relationship in predicting risk for cardiovascular diseases [28]. In this study, Glucose levels showed to be the strongest predictor of GGT levels, as explained by the amount of variance in the GGT levels. This finding is supported by studies by Fonseca et al., [26] and Sabanayagam et al [18], where GGT levels showed strong positive correlation with incidence of diabetes. The multivariate analysis indicated significant model fit between GGT levels, and the anthropometric indices and biochemical parameters. The amount of variance in the GGT levels that was explained by the predictors is 37.2%. These findings observed suggest that GGT can be used to predict risk of cardiovascular disease development since anthropometric indices, biochemical parameters such as the lipid profile parameters, obesity and abdominal obesity markers are associated cardiovascular disease risk Arjmand et al. [29]. The search for tools to be able to detect early moments of CVD development are very pertinent to the clinician because the primary and secondary preventive actions are required in order to arrest the negative development of CVD. Moreover, early markers of CVD will allow abrupt interventions in order to avert the commencement of the diseases or, at least, curtail their negative consequences [30]. In this study, ROC curve analysis of GGT in predicting its accuracy in diagnosing risk of coronary events showed an AUC of 75.81 (65.40 -86.22) with a cut-off of 37.90U/L. This means GGT therefore demonstrates a high accuracy, good sensitivity and a high specificity in predicting coronary events among the study participants. In another similar study by Sheikh et al. where the association of serum Gamma-Glutamyl Transferase and premature coronary artery disease was assessed, the area under the receiver operating characteristic curve for GGT was 80.9% (range 76.5–85.3) with a cut-off point of 22.5 IU/l, with a positive predictive value and negative predictive value for GGT being 71.3 and 79.3, respectively [31]. The findings in this present study showed total cholesterol, LDL cholesterol, triglyceride, were significantly associated with increased risk of developing any coronary events (**Table 4**). This is in concordance with reports from several studies which have indicated that elevated LDL cholesterol, diabetes and low HDL can predict premature coronary heart diseases [32–34]. Despite the fact that post-hoc sample size calculation recorded power of 85%; it should be mentioned there that, there were few limitations of the study. The inability to conduct cross-sectional study among lager population of diabetics which would have been a true representation of the diabetic population at followed up at Effia-Nkwanta regional hospital, the used of questionnaire to identify cofounder factors and inability to evaluate the gall bladder using ultrasonography. Notwithstanding, this is a baseline for further studies to address this interest.

Conclusion

This study showed that GGT has high accuracy in predicting the risk of cardiovascular diseases modelled by coronary risk events, thus GGT assay can be used as a predictive tool in assessing risk of cardiovascular disease development among diabetes mellitus individuals. The study also established an increase in GGT levels with increasing glucose concentration of the study participants.

Competing Interest

The authors declare that they have no competing interest.

Disclosure Summary

The authors have nothing to disclose.

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Author Contributions

CO contributed to the conception of the research idea, design data analysis and interpretation, paper drafting and revision. EA contributed to the conception of the research idea, design, data analysis and interpretation, paper drafting and revision. SA contributed to the conception of the research idea, analysis and interpretation, paper drafting and revision. ET contributed to

the collection data analysis and interpretation, paper drafting and revision. EOA and DG contribution to the collection and data analysis and interpretation. BA contributed to the conception of the research idea, analysis and interpretation, paper drafting and revision. ENB contributed to the data collection. All authors approved the final manuscript before publication and agree to be accountable for all aspects of the work.

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