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Moderate to Severe Renal Insufficiency among Individuals with Human Immunodeficiency Virus Infection in Tanzania

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Abstract

Background

Information about renal insufficiency and associated risk factors among people living with HIV (PLHIV) infection in East Africa is limited. The aim of this study was to determine the prevalence and factors associated with moderate to severe renal insufficiency among PLHIV in Dar es Salaam, Tanzania.

Methods

A cross-sectional analysis of the baseline clinical data for 30,822 PLHIV who enrolled at the Management and Development for Health - Care and Treatment Clinics (MDH-CTCs) in Dar es Salam, Tanzania was done. Moderate to severe renal insufficiency was defined as estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m^2 based on the CKD-EPI equation. Poisson regression models weighted by the inverse probability of inclusion in the study were used to estimate prevalence ratios for predictors of renal insufficiency.

Results

Our study population was relatively young [median age (IQR) of 35 (17-50) years], predominantly female (57% non-pregnant, 13.1% pregnant of all participants), and the majority (90.6%) were ART (Anti-Retroviral Therapy) naïve. The overall prevalence of moderate to severe renal insufficiency was 8.2%. In multivariable adjusted analysis, moderate to severe renal insufficiency was significantly associated with older age (i.e. ≥ 50 years) [Prevalence Ratio (PR) 2.16, 95% CI (1.70-2.75)], mid-upper-arm circumference under 22 cm [PR 1.48 (1.06, 2.07)], CD4+ cell counts of < 50 cells/mm^3 [PR 1.43(1.10-1.85)]; and WHO HIV/AIDS stage IV [PR 16 2.09(1.40-3.11)].

Conclusion

Moderate to severe renal insufficiency is prevalent among PLHIV enrolled at Care and Treatment Centers in Dar es Salaam, Tanzania. In particular, older patients with advanced HIV/AIDS stage and poor liver function are more likely to present with moderate to severe renal insufficiency. However, further studies to explore the causal relationship between these associated risk factors and the outcomes (renal insufficiency) are warranted.

Keywords: *Kidney disease, Risk factors, AIDS, HIV adult patients, Tanzania.*

Introduction

The sub-Saharan Africa (SSA) region remains the hardest-hit WHO region accounting for almost 80% of all people living with HIV/AIDS globally (1). Scaling up of antiretroviral therapy (ART) coverage has helped reduce disease progression and improved survival of people living with HIV/AIDS (2-4). The HIV infection per se, immunological reaction against it and nephrotoxicity of ART are some of the established factors that fuel developing of chronic kidney disease among HIV/AIDS patients in this region.

Non-communicable diseases (NCDs) are increasingly common among HIV-infected individuals as a result of improved survival and increased life expectancy from effective use of ART (5-7). Further; advancing age, smoking, excessive alcohol intake and physical inactivity all compound the risk of developing NCDs among people living with HIV (PLHIV). Chronic renal insufficiency is a progressive irreversible loss of kidney function over a period of time and is commonly seen among HIV-infected individuals. Chronic renal insufficiency appears to be more of a threat in Sub Saharan Africa, which is home to about 71% of people living with HIV/AIDS globally and where up to 75% of global HIV/AIDS deaths and 65% of global new HIV infections occur.

In Tanzania, mild and moderate renal insufficiency was found to be common among HIV-infected adults at the time of ART initiation (8-11). Morbidity and mortality from chronic renal insufficiency in sub–Saharan Africa are also significant due to poor access and affordability of renal replacement therapy (12, 13).

Despite being a growing problem in sub–Saharan Africa, population-based data on burden of kidney dysfunctions, chronic kidney disease, magnitude and risk factors are still very limited (14, 15). This study, based on a large cohort, reports on the prevalence of renal insufficiency among PLHIV and explores factors associated with renal insufficiency among HIV-infected individuals in Tanzania.

Methods

Study Site and Population

HIV-infected individuals aged 15 years or older were enrolled in HIV/AIDS Care and Treatment Centers (CTC) located in Dar es Salaam, Tanzania between October, 2004 and September, 2011. The study sites were CTC facilities in Dar es Salaam supported by Management and Development for Health (MDH), a leading non-profit public health organization that primarily focuses on public health service, education and research in the United Republic of Tanzania. All HIV/AIDS patients with measured serum creatinine, age and sex at first visit were included in this study. The estimated glomerular filtration rate (eGFR) as an outcome response was

calculated. Patients at the CTCs supported by MDH followed standard ethical oversight by the Tanzanian National Institute for Medical Research.

Study Design and Data Collection

This study was database (secondary data) review. A cross-sectional study design was used and data were collected from the time of enrolment at the MDH CTCs. Physicians and nurses at the CTCs completed the standard forms to record the socio-demographic details and additional information including type of facility at enrolment and calendar year of enrolment. Furthermore, clinical, laboratory, and detailed medical information such as CD4 T cell counts (cells/mm^3), body mass index (kg/m^2), clinical WHO stage, hemoglobin (mg/dl) level and serum alanine aminotransferase (ALT) (units/L) were also collected.

Estimation of Kidney Function

The estimated glomerular filtration rate (eGFR) which measures the kidney function was computed using a CKD-EPI formula which uses serum creatinine, black ethnicity, gender and age, variables which are easy to obtain accurately. The eGFR is used to monitor progression of the kidney disease over time and to stage chronic kidney disease into stages I to V; eGFR≥90ml/min/1.73m^2 (Stage I), eGFR between 89 – 60 ml/min/1.73m^2 (Stage II), eGFR between 59 – 30 ml/min/1.73m^2 (Stage III), eGFR between 30 – 15 ml/min/1.73m^2 (Stage IV) and eGFR< 15ml/min/1.73m^2 (Stage V) also referred to end stage renal disease. Generally, stages I and II (eGFR ≥60) are collectively referred to as mild kidney disease that requires evidence of kidney injury to establish the diagnosis, whereas stages III to V (i.e. eGFR< 60) are collectively (regardless of evidence of kidney injury) referred to as moderate to severe renal insufficiency. In this current study, since very few patients had serum creatinine levels taken 90 days after the first one (to satisfy the definition of chronic kidney disease), we prefer to use the term renal insufficiency to describe a one-time low eGFR, rather than chronic kidney disease (CKD). Further, although calculated kidney function is expressed in as ml/min/1.73m^2, for simplicity, this unit expression will be omitted whenever we refer to eGFR for the remainder of this article.

Statistical Analysis

The primary outcome in this study was moderate to severe renal insufficiency as described above. Variables routinely collected on CTC intake forms included age, gender, season at enrolment, district, year of registration, WHO stage, CD4 count, body mass index (BMI, kg/m^2), hemoglobin level, pregnancy status, 22 mid-upper arm circumference (MUAC), facility level, ALT and ART use prior to enrolment at the MDH-supported CTCs.

Continuous variables were also categorized based on conventional cutoff points. Age (years) was <30, 30 to <40, 40 to <50 or 50+. CD4 count (cell/mm3) was categorized as <50, 50-99,100-199 and ≥200. BMI (Kg/m^2) was categorized as <17, 17 to <18.5, 18.5 to <25 or 25+. MUAC (cm) was categorized as <22, 22 to <23, 23 to <27 or 27+. The health facility levels were dispensary, health centre, and hospital. ALT (IU/L) was categorized as <40, 41-120, 121-200, 201+. ART use prior to CTC enrolment could include use of prevention of mother to child transmission (PMTCT). Categorical variables were described by proportions (% of the whole study population). In routinely collected data sets of this sort, missing data are common. In order to keep all possible observations in our multivariable analysis, we made missing indicators for the appropriate categorical variables. Continuous variables were displayed as median (inter-quartile bounds). We refer to the quartile bounds as the interquartile range (IQR).

Since we were concerned about possible selection bias resulting from the fact that most of our potential subjects did not have a recorded value for serum creatinine at CTC enrolment, we used inverse probability of inclusion weighting. The logistic model used all available variables. Weights greater than the minimum of 100 or the third quartile + 3*IQR were set to that value, to avoid excessive influence of observations with extremely low predicted probabilities of having serum creatinine values. Univariate comparisons of the patients with and without serum creatinine measurements were done using the chi-squared test for categorical variables and the Wilcoxon or Kruskal-Wallis test for continuous variables (Table1).

Table1: Baseline characteristics of the study population at CTC enrolment in Tanzania (N=83,823)

Characteristics	Categories	Moderate to severe renal insufficiency (n=30822)	Indeterminate, normal or mild renal insufficiency (n= 53001)
Gender	Male	9223(29.9)	14447(27.3)
	Non-Pregnant Female	17577(57.0)	30898(58.3)
	Pregnant Female	4022(13.1)	7656(14.4)
Age group, median (IQR)		**35(12)**	
in years	<30	7564(24.5)	14561 (27.5)
	30 – <40	13480(43.7)	22468 (27.5)
	40 – <50	6807(22.1)	11085((20.9)
	50+	2971(9.6)	4887((9.2)
District at enrolment	Ilala	10825(35.3)	22179(41.8)
	Kinondoni	9941(32.5)	17937(33.8)
	Temeke	9850(32.2)	12251(23.1)

Facility Level at enrolment	Hospital	27217(88.9)	40988(77.3)
	Health Centre	2213(7.2)	4996(9.4)
	Dispensary	1186(3.9)	6683(12.6)
Blood Pressure Control [SBP/DBP), median (IQR), mmHg		**110(19), 70(16)**	
	<140/90 (Normotensive)	21600(89.7)	32906(62.1)
	≥140/90 (Hypertensive)	2480(10.3)	3105(5.9)
Glycemic Control, median (IQR), mg/dl		**71(31)**	
	<200 (Normoglycemic)	20620(99.2)	2340(4.4)
	≥200 (Hyperglycemic)	166(0.80)	20(0.04)
MUAC*, Median (IQR), cm		**25(5.5)**	
	<22	5398(18.7)	7090(13.4)
	22-<23	2444(8.5)	3535((6.7)
	23-<27	11760(40.7)	19268(36.4)
	>27	9330(32.3)	16644(31.4)
Hemoglobin level, median (IQR), g/dl		**10.3(3.1)**	
	<7	2406(8.7)	2046(3.9)
	7 – <8.5	3712(13.3)	3225(6.1)
	8.5-12	15118(54.3)	16583(31.3)
	>12	6583(23.7)	7479(14.1)
CD4 count, median (IQR), cells /mm^3		**178(279)**	
	<50	5818(20.1)	6440(12.2)
	50-100	3675(12.7)	4358(8.2)
	100-200	6093 (21.1)	7452(14.1)
	>200	13336(46.1)	23600(44.5)
WHO HIV clinical stage at enrolment (0 - 30 days)	I	6159(20.6)	12593(23.8)
	II	5334(17.8)	10207(19.3)
	III	12476(41.7)	20205(38.1)
	IV	5925(19.8)	7364(13.9)
Serum ALT level at enrolment, median (IQR), (U/L)		**19(16)**	
	≤40	26,481(87.2)	22684(42.8)
	>40-120	3,577(11.8)	2662(5.0)
	>120 - 200	231(0.8)	151(0.3)
	>200	89(0.3)	73(0.1)
Previous ART use at enrolment	No previous ART use	27,297(88.6)	43260(81.6)
	Previous ART use	2,813(9.1)	4989(9.4)
Stages of Renal Insufficiency ($mL/min/1.73m^2$)	I ≥90**	16764(54.4)	
	II 60-<90**	10669(34.6)	
	III 30-<60	2759(8.9)	
	IV 15-<30	484(1.6)	
	V <15	146(0.5)	

**MUAC= Mid Upper Arm Circumference.*

***Mild kidney dysfunction that requires other markers to establish presence of chronic kidney disease (e.g. proteinuria, abnormal kidney morphology on ultrasound etc).*

We estimated prevalence ratios (PR) and their 95% confidence intervals for both univariable and multivariable analyses using generalized estimating equations (GEE) with the log link and the Poisson distribution and weighted by the inverse probability of inclusion in the study, henceforth referred to as Poisson regression. For non-binary unordered categorical variables, the p-value shown was based on the robust score test. For ordered categorical variables, including those made from continuous variables, the reported p-value was based on the median-score trend test using only the non-missing categories.

As a check on our models, we also made models in which we (as an exaggeration) assigned no renal insufficiency to all the patients who did not have values for creatinine and used the same multivariable models with and without weighting.

Restricted cubic splines were used to plot non-parametric curves for all continuous covariates to assess the linearity of their association with the renal insufficiency for the purpose of making the figures. We examined the possibly non-linear relationship between our potential predictors and moderate to severe renal 4 insufficiency non-parametrically with restricted cubic splines (16). Tests for non-linearity used the robust score test for the hypothesis that the coefficients of all the spline variables were 0. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

From October, 2004 to September, 2011, 83,823 HIV-infected individuals aged 15 years or older were enrolled in four CTCs supported by MDH. For this study, we recruited 30,822 (36.8%) who had serum creatinine measured at enrolment. Using CKD-EPI equation for determining estimated renal function, we determined that 2530 (8.2%) patients of those recruited had moderate to severe renal insufficiency.

All univariable comparisons of the variables shown in Table 1 between those who had creatinine measurements and those who did not had p-values <0.0001, whether missing values were considered.

The multivariable logistic models with outcome ‘has creatinine value’ had area under the receiver operating characteristic curve (AROC) of 0.94 (near perfect prediction) for the model using all available variables.

Of the 30,822 individuals included in this analysis, over two-thirds were female (70.1%) and over two- thirds (68.2%) were aged 40 years or less with a median (IQR) of 35(17-50) years. Pregnant women comprised 13.1% of all participants in this study. Participants were evenly distributed across the three administrative districts of Dar es Salaam City and the majority (88.9%) of them were enrolled at Hospital-level Care and Treatment Centers. Among the

24,080 individuals with recorded blood pressure, 89.7% were normotensive. Among the 20,786 with recorded fasting or random blood glucose, and almost all (99.2%) of them had normal blood glucose levels.

Analysis of their clinical and laboratory characteristics at the time of enrolment showed that although the majority (90.6%) were still ART-naïve, 61.6 % had advanced HIV disease (WHO stage III and IV) and over half (53.9%) had CD4 cell counts of less than 200 cells/mm^3. Further, less than a quarter (23.7%) had hemoglobin levels of 12g/dl or more) while 8.7% had hemoglobin below 7 g/dl. The majority (87.2%) had serum alanine aminotransferase levels < 40U/L. Prevalence of moderate to severe renal insufficiency (eGFR <60) among individuals with HIV/AIDS at the time of enrolment was 11% among whom 146(0.5%) participants had eGFR <15.

Table 2 shows the results of the weighted univariable and multivariable Poisson regression analyses. Age showed a strong nonlinear trend (Fig 1a) whereas hemoglobin level (Fig 1b) showed and inverse trend for renal insufficiency. In multivariable adjusted analysis, moderate to severe renal insufficiency was significantly associated with older age (i.e. ≥ 50 years) [Prevalence Ratio (PR) 2.16, 95% CI (1.70-2.75)], mid-upper-arm circumference under 22 cm [PR 1.48 (1.06, 2.07)], CD4+ cell counts of < 50 cells/mm^3 [PR 1.43(1.10-1.85)]; and WHO HIV/AIDS stage IV [PR 16 2.09(1.40-3.11)]. In general, individuals who were less healthy were more likely to have moderate to severe renal insufficiency. The parameter mid upper arm circumference (MUAC) showed strong trends, with the thinnest individuals having the highest prevalence. Similarly, prevalence went up with severity of anemia. More severe HIV disease, as measured by either WHO HIV stage or by CD4 cell count, was also associated with higher prevalence.

Table 2: Factors associated with baseline moderate to severe renal insufficiency among individuals with HIV infection in Tanzania (N=30,822)

Characteristics	Univariate RR 95% CI	p-values	Multivariate RR 95% CI	p-values
Gender				
Male	Ref		Ref	
Non-Pregnant female	1.27 (1.22-1.32)	<0.0001	1.43 (1.29-1.58)	<0.0001
Pregnant Female	0.42(0.38-0.46)		0.75(0.57-0.99)	
Age group, years				
30 – <40	Ref		Ref	
<30	0.55(0.52-0.59)		0.62(0.54-0.71)	
40 – <50	1.36(1.30-1.42)	<0.0001	1.41(1.27-1.56)	<0.0001
50+	1.88(1.78-1.97)		2.03(1.80-2.30))	

District at enrolment				
Kinondoni	Ref		Ref	
Ilala	0.95(0.91-1.00)	0.0413	0.96(0.88-1.05)	
Temeke	1.12(1.07-1.17)		1.10(1.01-1.19)	<0.0001
Facility Level at enrolment				
Dispensary	Ref		Ref	
Health Centre	1.37(1.21-1.54)	<0.0001	1.46(1.14-1.87)	<0.0001
Hospital	1.69(1.54-1.86)		1.56(1.26-1.96)	
MUAC group, cm				
<22	Ref		Ref	
22-<23	1.43(1.35-1.51)		0.97(0.84-1.11)	
23-27	1.33(1.24-1.42)	<0.0001	0.98(0.83-1.16)	0.5
≥27	1.08(1.03-1.13)		0.98(0.88-1.10)	
Hb group, kg/m^2				
>12	Ref		Ref	
8.5-12	1.18(1.11-1.25)		1.07(0.92-1.25)	<0.0001
7 – <8.5	1.98(1.85-2.11)	<0.0001	1.61(1.36-1.91)	
<7	2.93(2.75-3.13)		2.43(2.04-2.90)	
CD4count, cells/mm^3				
200+	Ref		Ref	
100– <200	1.48(1.40 – 1.56)		1.22(1.08 – 1.38)	
50 – <100	1.80(1.69 – 1.91)	<0.0001	1.39(1.21 – 1.59)	<0.0001
<50	2.14(2.04 – 2.25)		1.61(1.43 – 1.59)	
WHO HIV/AIDS stage				
I	Ref		Ref	
II	1.69(1.55-1.85)	<0.0001	1.33(1.09-1.63)	<0.0001
III	2.31(2.14-2.49)		1.56(1.30-1.86)	
IV	3.39(3.14-3.65)		2.07(1.72-2.50)	
ALT Category at enrolment (U/l)				
40 or less	Ref		Ref	
41-120	1.41(1.34-1.48)		1.37(1.23, 1.54)	
121-200	1.80(1.54-2.12)	<0.0001	1.42(1.01, 2.01)	<0.0001
201+	1.54(1.15-2.07)		1.66(1.01, 2.72)	
Previous ARV use				
Used for PMTCT& others	Ref	0.07	Ref	0.3
None	0.91(0.82-1.01)		1.07(0.96,1.19)	

RR, relative risk; BMI, Body mass index; WHO stage, World Health Organization HIV disease stage;
ALT, Alanine Aminotransferase; ARV, Antiretroviral Virus, PMTCT, Prevention of mother to child transmission of HIV.
Level of significance used (α=0.05)

Alternate models, including using all the individuals and assigning no renal insufficiency to those who did not have a serum creatinine value also showed the same trends in both weighted and unweighted analysis.

Discussion

This present study shows that moderate to severe renal insufficiency is already prevalent among PLHIV at the time of enrolment at the CTC, advanced age, poor nutritional status, and advanced HIV disease are independent predictors of presenting with renal insufficiency among PLHIV.

This study reports a high prevalence ratio (8.2%) of moderate to severe renal insufficiency among PLHIV that is comparable to similar studies done in the region. Although a recent meta-analysis shows a high prevalence of chronic kidney disease in Africa (16%), prevalences of 3%, 4% and 30% have been reported in Mozambique, Kenya and Zimbabwe, respectively. These reported variabilities may be due to different aging and survival trends, use of ART (9.4% in our cohort), presence of comorbidities (such as hypertension and diabetes) and use of different methods for assessment of renal insufficiency (17-20).

As more HIV-infected adults survive longer due to universal accessibility and effective ART therapy, the prevalence and incidence of renal insufficiency will increase, contributing to poor quality of life and morbidity in these PLHIV, largely related to the multi organ-systemic involvement of chronic uremia caused by declining kidney function. For low- and middle-income countries of the SSA region with restricted health budgets and resources, this double burden of renal insufficiency and HIV is a heavy public health challenge largely because of restricted availability and access to renal replacement therapy and the high cost associated with it.

Advancing age is a major risk factor for renal insufficiency (18-21). Adults aged 50 years or more in this study had a twofold increased risk of moderate to severe renal insufficiency mirroring increased prevalence with age observed in the general population (22). Several other previous studies that involved PLHIV have reported that advanced age was associated with increased risk of renal insufficiency (23-26).

Advanced stages of HIV infection reflect significant immune dysfunction that pose increased risk for progressive renal insufficiency among these PLHIV. Those with CD4 T cell count < 50 cells/mm^3 had a 61% greater risk for renal insufficiency, similar to other studies. In animal models (primates and rodents), HIV-1 infection (through expression of deleterious viral genetic products) has been associated with renal injury pathway contributing in development of progressive chronic kidney disease. Furthermore, there is a strong evidence from *in vivo*

studies that both renal glomerular and tubular epithelial cells harbor HIV-1 nucleic acids (26) however, *in vitro* studies exploring on the same have yielded inconclusive results on the increased susceptibility of the glomerular cells to HIV infection (26).

In this study, we found that hemoglobin is inversely related to renal insufficiency. Previously, it has been reported that low hemoglobin increases the risk for renal insufficiency (27). Mechanistically, low hemoglobin increases the risk for hypoxia of renal tubular epithelial cells which plays a significant role in pathogenesis and progression of renal insufficiency (28). Further, uremic toxin accumulation induces hemolysis that in turn worsens the hemoglobin concentration(29). Also, deficiency of erythropoietin is at least in part, associated with microvascular disease that leads to production of inflammatory mediators such as interleukin1(IL-1) and tumor necrosis factor (TNF) which has an effect on the bone marrow erythroid precursors(30). This study suggests that low hemoglobin (usually when eGFR<60) should be considered as a harbinger of renal insufficiency among PLHIV (31).

The increase in serum ALT level was associated with the increased risk of renal insufficiency. Serum ALT level is considered a marker of HIV-related inflammation, along with oxidative stress; it may lead to an increased risk of HIV related kidney dysfunction. This study found the increased risk of renal insufficiency among PLHIV with serum ALT level concentration > 40 units/L. In this study, previous use of ART was low in this study and antiretroviral toxicity is unlikely to have influenced the association between serum ALT level concentrations and increased risk of renal insufficiency. A previous follow up study in Tanzania observed a trend towards renal improvement in HIV-infected adults who received tenofovir-containing regimens and were reported to support safety use of ART with mild to moderate renal dysfunction(10).The major strength of this study was the use of large sample size compared to previous studies which were done inside and outside SSA, and the larger number of risk factors that were possible to assess and to include in adjusted analysis models. The use of the CKD-EPI equation which is a validated and highly reproducible formula for assessing the kidney function makes findings from this study easily comparable with similar studies done elsewhere.

Nonetheless, this study has some limitations worthy pointing out. A significant proportion of study participants lacked recorded serum creatinine values, this might under or overestimate the reported prevalence. Further, for individuals aged between 15 and 18 years, the use of CKD-EPI (instead of the recommended Modified Schwartz formula) may have led to inaccurate estimated renal function in this age bracket. The observational and cross-sectional design of this study raises the possibility of residual confounding and reduces certainty about causal inference of the findings. Lack of data on proteinuria and risk factors specific to SSA

(e.g., viral hepatitis, herbal use) limits further analysis to tease out the effect of potential specific confounders.

In conclusion, in this study we report a high prevalence of moderate to severe renal insufficiency among the HIV-infected adults. Our findings should remind clinicians that routine screening for kidney function among HIV-infected adults at enrolment is important for early recognition of kidney dysfunction. Special attention should be directed to PLHIV enrolling at CTC with advanced age, anemia, deranged liver function and advanced HIV disease as these factors were determined to be independently associated with moderate to severe renal insufficiency.

Identifying these PLHIV early on and managing them in close liaison with a nephrologist, abrogates and decelerate the rate of progression into end stage renal disease that demands renal replacement therapy (dialysis therapies and/or kidney transplantation) which is both very costly and of limited accessibility especially in the SSA region.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from participants during primary data collection. PLHIV at the CTCs supported by MDH followed standard ethical oversight by the Tanzanian National Institute for Medical Research.

Consent for publication

Not applicable.

Availability of data and materials

The dataset generated and/or analyzed during the current study are available from the Corresponding Author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

PJR, IKA, JJR and DMS were involved with the analysis and drafting of manuscript, IIA revised the drafting of the manuscript whereas EH, DS, FMM and FWW supervised the drafting of the manuscript. All authors contributed to the revision of the manuscript and approved the final version.

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