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Abnormal hematological indices and anthropometric parameters associated with type 2 Diabetes

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Abstract

Background: Hematological changes influencing blood cells are appeared to be related with type 2 diabetes mellitus is commonly associated with vascular complications. In recent years, there has been renewed interest and increasing evidence that hematological abnormalities can be used as indicators of endothelial dysfunction and inflammation in T2DM. Hence aim of this study was to assessments of abnormal hematological indices and anthropometric parameters associated with type 2 diabetes.
Methods: This study involved 70 people with T2DM (male/females, 47/23) and 70 age and sex matched Healthy people without T2DM (Male/females, 46/24). Anticoagulated blood samples were collected from fasting individuals and hematological Indices analyzed by automated blood cell counter and fasting blood sugar by automated chemistry analyzer.
Result: Male people with T2DM were characterized by significantly elevated levels of; body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean cell hemoglobin (MCH), red blood cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), FBS ($P<0.05$) as compared with healthy people without T2DM group. Similarly, female people with T2DM were characterized by significantly elevated levels of DBP, HCT, MCHC, RDW, WBC, PLT, MPV, PCT, and FBS ($P<0.05$) as compared with non-diabetic female control. .
Conclusions: This examination demonstrated statistically significant difference in some hematological parameters of diabetic patients compared with controls. Thus, hematological indices could be useful indicators diabetic complication in type 2 DM patients
Keywords: Diabetes, oxidative stress, hematological abnormalities, vascular complications.

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1. Introduction

The world has gained great ground in reducing deaths from the infectious transmittable malady, however, this achievement has made ready for the pandemic of non-communicable disease (NCD). NCD, particularly cardiovascular malady, diabetes, chronic obstructive pulmonary disease, and a few malignancies, now represent 57 million deaths and 15 million deaths were premature (30 to 70 years). The death happens in low-and middle wage nations, where 78% of all NCD deaths and 85% of premature deaths occurred [1]. All inclusive, the pervasiveness of Diabetes Mellitus (DM) is 8.5% and it is assessed that one of every 10 adults will have DM on the world by 2035 [2]. Sub Saharan African nations are relied upon to encounter the quickest increment in the number of individuals living with type 2 DM in the following two decades overall. Ethiopia is the third most fast growing nation in the African continent with 5.2 % prevalence of DM [3].

Type 2 diabetes is the main source of microvascular intricacies and presents an overabundance danger of cardiovascular malady and death [4, 5]. Microvascular and macrovascular difficulties frequently happen correspondingly and share comparable hazard factors and obsessive pathways [6, 7].

The nearness of microvascular ailment expands the danger of cardiovascular grimness and mortality in individuals with type 2 diabetes, free of the major built-up cardiovascular hazard factors [8]. Cardiovascular intricacies are frequently present as of now at the season of the finding of T2DM and subjects with impaired glucose tolerance have a roughly twofold increment in the danger of macrovascular ailments [9]. Ethiopia is confronting a double burden problem because type 2 DM is right now expanding because of various factors, for example, aging, urbanization, and obesity. Despite the fact that the rate composes 2 DM and its related vascular complexities are rising, current information about the issue is limited [10].

Recently, there has been reestablished enthusiasm for hematological parameters, for example, white blood cell (WBC), mean platelet volume (MPV), platelet distribution width (PDW), platelet crit (PCT) are assigned as indicators of endothelial dysfunction and chronic inflammation.DM is considered as a "prothrombotic state" inferable from hyperglycemia, dyslipidemia, and insulin resistance causing endothelial and pericyte damage. Modified platelet morphology and capacity has been seen in diabetes as improved platelet activities which may add to this "prothrombotic state". Increased white blood cell count (WBC) is an established marker of cardiovascular diseases in diabetes. Moreover, the relationship of raised MPV, PDW, PCT and platelet counts associated with endothelial dysfunctions, metabolic disorder, diabetes, coronary artery disease and malignancy have been indicated [11-15].

Hematological indices being a basic, economic test, done as a part of complete blood cell counts in a recent time of automated blood analyzers can be checking the patients for hematological abnormalities and subsequently expanded to thrombogenicity. It is underlined that it tends to be exceptionally basic, fast and cost-effective tool, particularly in developing nation like Ethiopia with constrained assets to distinguish early vascular complications in diabetic patients.

Hence the goal of this investigation is to decide to assess hematological profile among T2DM and compared with non-diabetic controls. This examination may be elucidated by the relationship between hematological indices and diabetic complications.

2. Materials and Methods

2.1 Study area, design, and period

Hospital-based, cross-sectional study with comparative nature was conducted on people with T2DM in the Federal police Specialized Hospital, Addis Ababa, and Ethiopia. All adult people with T2DM out patients in federal police specialized hospital (FPSH) and healthy people without T2DM were consisted in the study and were randomly selected from the police members.

2.2 Study population

This study included all adult people with T2DM (>18 years of age) attending federal police specialized hospital (FPSH) outpatient department in the time interval of the study period. However, T2DM people with a history of known hematologic diseases like; hemolytic anemias, post-hemorrhagic anemia, renal anemia, Hematologic diseases with WBC count > 15,000/mm^3 and platelet count > 500,000/mm^3 that may affect hematological profiles were excluded from the study.

2.3 Sample Size Determination

The required sample size was determined using single population formula for estimating single population proportion. Avoid error in non response rate, 10% of the calculated sample size was added. Therefore, the total sample was; n = 64.08+10% (64.08) = 64.08+6.408 ≈ 70**.**

2.4 Variables

Hematological profiles like; RBC, Hemoglobin, Hematocrit, MCH, MCHC, Red blood cell distribution width (RDW), WBC, PLT, Mean platelet volume (MPV), Platelet distribution width (PDW) and Platelet Crit (PCT) were considered as dependent variables of this study. On the other hand, anthropometric and clinical characteristics like; Age, Sex, Body mass index (BMI), systolic blood pressure (SBP), Diastolic blood pressure (DBP) and duration of diabetes were also taken as independent variables.

2.5 Blood sample and data collection procedures

After the study participants had been asked for their consent to be interviewed and to give a blood sample, about 2 ml of the blood was withdrawn from the study participants, who had fasted overnight and collected in EDTA-coated tubes and hematological profiles were determined for all samples using hematological analyzer (automated cell-dyne 1800). The blood sample was collected by qualified healthcare professionals in the hospital for immediate laboratory analyses. The collected blood was immediately analyzed to protect blood cells from hemolysis. In addition, the questionnaire was filled with a face-to-face interview, and some anthropometric indicators were also assessed and measured side by side as well.

3. Results

3.1 Anthropometric and clinical characteristics

The anthropometric and clinical characteristics of the patients and controls were illustrated in **Table 1**. The study showed statistically higher values of body mass index (BMI, P=0.001), systolic blood pressure (SBP, P=0.002) and diastolic blood pressure (DBP, P=0.019) with no difference in the mean age (P>0.05) of male T2D patients. However, there was no significant difference in the mean values of age, BMI and SBP (P>0.05) but higher values of DBP (P=0.008) was observed in female patients.

3.2 Platelet indices

Analysis of the platelet indices in male patients had statistically higher values of platelet count (PLT, P=0.024), mean platelet volume (MPV, P=0.000) and platelet distribution width (PDW, P=0.001) with no change in the mean values of platelet crit (PCT, P=0.603).

Similarly, female patients had remarkably elevated values of platelet indices like PLT count (P=0.000), MPV (P=0.000) and PCT (P=0.005) with no difference values in PDW (P=0.154) **Table 2.**

3.3 RBC indices

The mean values of the RBC indices indicated in **Table 3**. In the male subjects showed that, the mean values of red blood cell distribution width (RDW, P=0.001), mean cell volume and mean cell hemoglobin (MCH, P=0.03) were notably elevated. On the other hand, comparison of female subjects revealed that, HCT (P=0.005), RDW (P=0.012) and MCHC (P=0.015) were remarkably elevated. Similarly, numerically higher values of HGB (P=0.057) and MCV (P=0.271) but lower RBC count (P=0.863) was observed in female patients.

3.4 White blood Cell (WBC) indices

As indicated in **Table 4** the results of the present study showed that, there were no significant differences observed in the average values of WBC count (P=0.09), Neutrophil (Neu, P=1.532), Lymphocyte (Lymph, P=0.329) and mixed cells (MID, P=0.088) in male patients. Female patients had significantly higher average levels of WBC count (P=0.000) with no statistical difference in the mean values of Neu, Lymph and MID (P>0.05).

3.5 Correlation Analysis

As indicated in table below, SBP, DBP, and RBCs were negatively correlated with MPV and this correlation was not statistically significant. However, PDW was positively and significantly (P=0.001) correlated with MPV.

Table 1: Comparison of the Anthropometric and Clinical Characteristics of Male/Female Patients with Male/Female healthy individuals

Variable name	Males (Mean ± SD)		p-value	Females (Mean ± SD)		P-value
	Patient (N=47)	Control (N=46)		Patient (N=23)	Control (N=24)	
Age(years)	53.17±11.64	53.07±10.17	0.96	49.7±9.89	47.88±8.38	0.499
BMI(Kg/m^2)	25.47±2.64	23.43±2.88	**0.001**	27.52±3.95	25.38±4.567	0.092
SBP(mmHg)	125.74±11.56	119.13±8.39	**0.002**	124.78±10.39	120.83±8.3	0.156
DBP(mmHg)	82.23±8.65	78.26±7.4	**0.019**	83.48±7.141	77.92±6.58	**0.008**
FBS(mg/dl)	152.79±68.48	97.67±12.90	**0.001**	165.13±53.51	95.29±7.937	**0.001**
DMD (years)	8.21±7.45	-		7.30±4.46	-	-

Results are presented as mean ± standard deviation and P<0.05 is statistically significant (indicated in bold).
SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, BMI - Body mass Index, DMD - Duration of Diabetes.

Table 2: Comparisons of the Platelet indices in Male/Female Patients with Male/Female Healthy individuals

Variable name	Males (Mean ± SD)		P-Value	Females (Mean ± SD)		P-value
	Patient (N=47)	Control (N=46)		Patient (N=23)	Control (N=24)	
PLT(x10^3/L)	310.64±160.72	251.46±69.26	**0.024**	336.43±64.49	247.04±64.82	**0.001**
MPV(fL)	10.87±1.69	9.47±1.34	**0.001**	10.6±1.36	9.08±1.122	**0.001**
PDW(10(GSD))	16.93±0.27	16.21±0.54	**0.001**	16.51±0.59	16.21±0.81	0.154
PCT (%)	0.26±0.05	0.25±0.06	0.603	0.29±0.07	0.24±0.06	**0.005**

Results are presented as mean ± standard deviation and P<0.05 is statistically significant (indicated in bold). PLT - Platelet count, MPV - Mean Platelet volume, PDW - Platelet distribution Width, PCT – Platelet Crit, fL-femtolitre, GSD-Geometric standard deviation.

Table 3: Comparisons of the RBC indices in Male/Female patients with Male/Female Healthy individuals

Variable name	Males (Mean ± SD)		P-Value	Females (Mean ± SD)		P-value
	Patient (N=47)	Control (N=46)		Patient (N=23)	Control (N=24)	
RBC(x10^6/L)	5.64±0.568	5.78±0.417	0.167	5.39±0.499	5.42±0.504	0.863
HGB(g/dL)	16.55±1.417	16.35±0.924	0.413	15.17±1.267	14.54±0.932	0.057
HCT (%)	51.21±3.967	50.52±2.681	0.329	47.70±3.430	45.29±1.899	**0.005**
MCH(pg)	29.72±2.534	28.78±1.413	**0.03**	28.30±2.285	28.46±1.179	0.771
MCHC(g/dL)	32.33±0.967	32.19±1.056	0.523	31.61±0.583	32.21±0.977	**0.015**
RDW (%)	14.28±1.862	12.76±0.993	**0.001**	14.04±1.397	13.08±1.10	**0.012**

Results are presented as mean ± standard deviation and P<0.05 is statistically significant (indicated in bold).
RBC-red blood cell count, HGB-hemoglobin, HCT- hematocrit, MCH- mean cell hemoglobin, MCHC- mean cell hemoglobin concentration, RDW- red blood cell distribution width, g/dl – gram per deciliter, pg - picogrem

Table 4: Comparisons of the WBC and Platelet indices in Male/Female patients with Male/Female Healthy individuals

Variable name	Males (Mean ± SD)		P-Value	Females (Mean ± SD)		P-value
	Patient (N=47)	Control (N=46)		Patient (N=23)	Control (N=24)	
WBC(x10^3/L)	6.77±1.844	6.20±1.31	0.09	7.48±1.620	5.83±1.007	**0.001**
Neu(%)	58.04±8.645	60.83±4.281	1.532	60.13±7.665	60.63±3.797	0.779
Lymph(%)	33.28±8.428	31.22±3.514	0.329	32.04±7.119	31.63±2.716	0.79
MID(%)	8.49±1.53	7.96±1.445	0.088	7.74±1.544	7.83±1.736	0.845

Results are presented as mean ± standard deviation and P<0.05 is statistically significant (indicated in bold).
WBC- white blood cell count, Neu- Neutrophil, Lymph- Lymphocyte, MID- Mixed cell

Table 5: Pearson correlations of MPV with various parameters in diabetic individuals

Variable name	Diabetic Patients	P- value
	Correlation **(r)** N=70	
DBP	-0.001	0.995
SBP	-0.008	0.946
RBC	-0.137	0.258
RDW	0.129	0.286
PDW	0.373	**0.001**

Results are presented as mean ± standard deviation and P<0.05 is statistically significant (indicated in bold).

4. Discussion

The present study revealed, statistically higher values of BMI in male and only a numerical difference in female people with T2DM. This is in consonance with Bukhari *et al* who reported higher values in both male and female people with T2DM [16]. Similarly, Sarah *et al* demonstrated significant values of BMI in T2DM patients [17]. Ganz *et al* suggested that, BMI is strongly and independently associated with the risk of T2D and the magnitude of this association is larger for higher BMI values [18].

Our finding of the blood pressure shows that SBP was significantly higher in males but not in females with T2DM. However, DBP was significantly higher in both males and females with T2DM compared to the corresponding values in their respective healthy people without T2DM. This result is in agreement with the findings of Alao *et al*; Bukhari *et al.,* who reported significantly higher values of both SBP and DBP in both sexes of people with T2DM [16, 19]. Hyperglycemia causes microvascular complications in many organs including diabetic nephropathy the leading cause of end-stage renal disease (ESRD) in developed countries [20]**.** In addition, Gurley & Coffman suggested that diabetes may lead to other vascular complications, including systemic hypertension through activation of the intrarenal rennin -angiotensin system [21]. As reported by He *et al.*, the metabolic receptor G-protein coupled receptor 91 (GPR91) is highly expressed in the kidney and activated by the citric acid cycle intermediate succinate because succinate is locally accumulated in the intact diabetic kidney [22]. Toma and his colleagues suggested that, high glucose and succinate-induced GPR91 activation trigger paracrine signaling from the (juxta) glomerular endothelium to the adjacent rennin producing JG cells to increase rennin synthesis and release the rate-limiting step of RAS activation [23]. This may explain elevated values of Systolic (SBP) and diastolic (DBP) blood pressures in the present study. On the other hand, increased SBP and DBP in patients of this study may be explained in terms of advanced glycation end products (AGE). It has been suggested that AGE and its cell surface receptor (RAGE) are the typical molecular consequence of diabetes [24]. AGEs also quench NO (nitric oxide) in vitro and may reduce NO-dependent vasodilatation. It also induced the production of the vasoconstrictor endothelin-1 by endothelial cells through nuclear factor-kB activation [25]. Therefore, since endothelin-1 is a potent vasoconstrictor, it increases the systemic blood pressure.

In this study, analysis of the platelet indices demonstrated that mean platelet volume and platelet counts were significantly higher among both sexes in people with T2DM. This is in corroboration with the studies conducted by, Kodiatte *et al*.,; Demirtas *et al*.,; Alhadas *et al*., [26,27,28]. In contrast, Hekimsoy *et al*., reported the remarkably low level of platelet count in people with T2DM [29]. The MPV and platelet counts are indicators of thrombotic potential and risk factors for microvascular complications in diabetes [30, 31]. According to Chen *et al* increased insulin resistance and glycemic status increases platelet count in hyperglycemia [32]. Taniguchi *et al*, has been indicated that increased platelet count may independently predict insulin resistance among non-obese Japanese type 2 DM patients [33]**.** Platelet size is another aspect that deserves attention because it seems to be related to their function. It has been demonstrated that, platelets with greater volume are younger, more reactive and aggregatable. Hence, they contain denser granules, secrete more serotonin and β-thromboglobulin, and produce more thromboxane A2 leading to increased thrombotic potential when compared with smaller and less active platelets [25, 27]. Thus, large circulating platelets are reflected by an increase in MPV which is the indicator of the average size,

a marker of platelet function and activity. In diabetic patients, higher level of MPV could predict an increased risk factor for thrombosis and chronic complications [28, 34, 35].

Elevated levels of MPV in people with T2DM of the present study may also be explained in terms of oxidative stress. Increased ROS in diabetes induces nonenzymatic glycation of proteins on the surface of the platelet [36]. Such glycation leads to over-accumulation of advanced glycation end products (AGEs)[37,38]. Some of these AGE cause externalization of platelet membrane phosphatidylserine that may cause changes in protein structure (conformation) and alterations of membrane lipid dynamics [39,40]. This may also explain the increased values of MPV in patients of the present study.

Regarding PDW, the present study showed that there was no significant difference between female people with and without T2DM. However, we observed that male with T2DM had significantly elevated values of PDW. According to Vagdatli *et al*, activated platelets undergo a structural change from discoid to a spherical shape and produces pseudopodia leading to a change in the PDW [41]. Due to this reason, activated platelets may be different in size from non-activated platelets. PDW has also been reported as significantly elevated in people with T2DM with complications when compared with people with T2DM without complications [28,40]. Thus, different sizes of platelets can be found, a consequence of which was the enlarged histogram plotting of PDW and increased levels of PDW [27,40].

Plateletcrit (PCT) is the other platelet parameter which has no significant difference in males, however, the significant elevation was observed in females with T2DM of the present study. This is in agreement with, Alhadas *et al*., [28]. In normal individuals, when platelet volume is increased, platelet count tends to decrease in order to maintain the values of PCT within normal ranges. Thus, platelet mass or PCT must be kept at constant levels**.** However, in people with T2DM, platelets become larger and more reactive through different mechanisms leading to the increased platelet mass thereby increasing PCT. According to Alhadas *et al*., this parameter was significantly elevated when there is a chronic complication. In general Platelet indices (PLT, PCT, MPV, and PDW) are determinants of platelet functionality, among which MPV and PDW stand out due to their involvement in the development of thromboembolic complications [28].

Our data demonstrated that RBC count was lowered in people with T2DM of both genders but this difference was not statistically significant. Wang *et al.,* suggested that decreased RBC count is an independent predictor of the risk of microvascular complications in people with T2DM and this is mediated partly through an effect of decreased RBC count on RBC function [42].

Decreased RBC count in this study may be explained in terms oxidative stress which can result in the mechanical alterations of RBC membrane protein. Altered membrane proteins are associated with the development of microvascular complications in diabetes. The biconcave discoid shape of RBC is maintained by the membrane cytoskeleton which is known to be the major determinant of the cells dynamic behavior. Normal RBCs tend to orient themselves with flow streamlines under high shear (deforming) forces implying that, these cells are highly deformable bodies. They also behave as elastic bodies because the shape change is reversible when deforming forces are removed [43]. The most important component of the RBC membrane cytoskeleton network (network of proteins lying beneath the cell membrane) is a protein called spectrin. However, in diabetes chronic hyperglycemia causes a non-enzymatical glycosylation of spectrin network for further oxidation leading to erythrocyte membrane abnormalities and accelerated aging of RBCs[43,44]. This might be responsible for increased impairment of RBC deformability among people with T2DM.

Hyperglycemia increase generation of superoxide anion that may cause several structural and functional modifications of the RBCs. One of the major modifications in this context is the aggregation and attachment of hemoglobin to the inside of the RBC membrane which is a cytoskeletal spectrine protein network [45). This may result in the alteration of the cell shape and mechanical properties of RBCs. hemoglobin attachment to spectrin network also increases the intracellular or cytosolic viscosity of the erythrocytes which is related to the mean cell hemoglobin concentration (MCHC)[42,43]. In this present study, MCHC was elevated in people with T2DM and the difference was statistically significant in females and insignificant in males. Increased MCHC may result in the reduction of RBCs membrane flexibility (deformability) and increase the membrane rigidity[44]. Reduced deformability may result in the complete standstill of RBCs moving through capillary segments that may lead to increased thrombogenic state and then atherosclerosis.

Regarding RDW our data revealed that the parameter was remarkably elevated in people with T2DM of both genders corroborating the results of Nada, 2015[46]. RDW is a quantitative measure of the red blood cell volume (RBCV) heterogeneity. Thus the higher the values of RDW are the greater heterogeneity in cell sizes [45]. Chronic inflammation and increased oxidative stress in diabetes cause the impairment of erythropoiesis and degradation of RBCs by fragmentation or agglutination related to anisocytosis [47]. This may shorten the RBCs lifespan

leading to decreased RBC count (49) which may also explain the result of the present study. It has been shown that increased RDW is an independent predictor of the overall and cardiovascular mortality in the general population and in those with various high risks [45]. Diabetes is thus, a known disorder that reduces the lifespan of RBCs resulting in the increased variability of the RBC volume (RDW). Increased RDW causes impairment on RBCs deformability and negatively affects blood flow through microcirculation because of the complete standstill movement of RBCs[42,46]. This may result in the increased thrombogenic state and atherosclerosis.

Our data showed a numerical difference of hematocrit (HCT) value in male and a significant elevation in female people with T2DM. The possible explanation for this is that increased sugar level increases the blood osmolarity and capillary permeability in diabetes. This may result in the increased hematocrit value and subsequently blood viscosity. Cho *et al* suggested that hyperglycemia may cause an osmotic diuresis and hence may lower plasma volume leading to increased hematocrit[45]. HCT is one of the major determinants of whole blood viscosity (WBV) because the level of HCT is positively associated with the level of WBV. Thus, HCT increases blood viscosity [44]. Abnormally high blood viscosity is known to play a role in aggravating myocardial ischemia by diminishing oxygen delivery due to atherosclerotic plaque at the coronary artery. Elevated blood viscosity also increases injurious forces at the endothelial wall and adversely affects the endothelial function. Increased HCT through a mechanism of increasing blood viscosity contributes to the inflammatory process and may increase the thrombogenic states [48]. Thus, increased HCT value in the present study may suggests that, HCT is also considered as one of the hematological profiles which may contributes to cause atherosclerosis when elevated.

The present study demonstrated that the significant elevation of Platelet parameters such as PLT, MPV in both sexes but RDW only in male but not in the female. In contrast PCT elevated in female but not in the male. Total WBC was elevated in female but not in male patients and decreased total RBC may strengthen the notion that the parameters are considered as inflammatory markers. This suggests that hematological parameters might be a useful prognostic marker of cardiovascular complications and thus used in control of T2D disease progression. Therefore, they may contribute to the early detection of complications and may have a role in the potential reduction of morbidity and mortality in diabetic patients. This study in Ethiopian population can be considered as an initial one that necessitates further studies to define the relation between hematological parameters with its prognostic value and different diabetic complications.

Declarations

Ethics approval and consent to participate

All participants in the study had information on the study. A consent form was prepared with a detailed explanation of objectives, risks, and benefits to the study subjects and the assurance of confidentiality of responses were given to participants. Assurances were given to the participants on the confidentiality of collected data. The project proposal was reviewed and approved by the Ethics and Research Review Committee of the Departments of Biochemistry (DRERC) that was approved on meeting No. DRERC: 03/15 protocol number 07/15 and Ref. No. SOM/BCHM/29/2007. Samples and data were collected after written informed consent had been obtained from study participants. Confidentiality, anonymity, neutrality, accountability, and academic honesty were maintained throughout the study.

Consent for publication

As a major aspect of the informed consent process, all members in this examination gave the exploration group consent for their information to be recorded, interpreted, anonymised, investigated and utilized in the arrangement of any logical distribution.

Availability of data and materials

The datasets produced are available online in the repository of the Addis Ababa University Library in the form of a thesis.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This work was carried out in collaboration between all authors. Author CO carried out all kinds of experimental parts and statistical analyses of data and managed the literature searches. Authors DS, MKCM and NG wrote the research protocol, worked in the analysis of data, wrote the first draft of the manuscript, and managed the literature searches. The latter also supervised the research work.

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