

Variables Associated with Low Muscle Mass Among End-Stage Renal Disease Patients Submitted to Hemodialysis: A cross-Sectional Study

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Research article

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Abstract

Background: We aimed to compare lean tissue index between patients with low and normal muscle strength in order to determine a cutoff to classify low muscle mass and find variables associated with low muscle mass among end-stage renal disease patients undergoing hemodialysis.

Methods: We studied 245 end-stage renal disease patients on hemodialysis in the only two dialysis centers located in the north region of Ceará state, Brazil, in October 2019. Demographic, clinical, laboratory and anthropometric measurements were collected. Patients' functional ability was assessed by the Brazilian version of the Stanford Health Assessment Questionnaire Disability Index. Bioimpedance analysis and handgrip testing were used, respectively, to evaluate lean tissue index and muscle strength. We classified low muscle mass according to muscle strength, and compared variables between patients with normal and low muscle mass. Variables that differed in the comparison were analyzed with a logistic regression model to detect independent predictors of low muscle mass.

Results: According to a cutoff of less than or equal to 15 kg/m² of lean tissue index to classify low muscle mass, we found a prevalence of 41.2% of low muscle mass. Patients with low muscle mass presented higher prevalence of functional disability. In multivariate logistic regression (considering low muscle mass as a dependent variable), age (older), female gender, creatinine level, fat tissue index and abnormal waist-to-hip ratio were found to be independent predictors of low muscle mass. **Conclusions:** Older patients, women, patients with low creatinine, with high fat tissue index and with abnormal waist-to-hip ratio should be classified as at risk of low muscle mass. Dietary improvements, encouragement of resistance exercise and the use of androgens should be tried in this group of patients. **Keywords:** End-stage renal disease, Hemodialysis, Sarcopenia, Muscle mass, Muscle strength, Bioimpedance, Handgrip test

Background

Low muscle mass is well studied in the general population, especially among the elderly. Among Brazilian healthy elderly people with mean age of 69.6 years, the report of low muscle mass is 33.6% [1]. In end-stage renal disease (ESRD) patients, even in a sample of younger hemodialysis (HD) patients (mean age of 53 years), there was 44% prevalence of low muscle mass [2]. The reason for such high prevalence of low muscle mass even in young people submitted to HD is the extensive list of factors associated with ESRD that provoke muscle wasting, like inflammation, metabolic acidosis, vitamin D deficiency, possible role of angiotensin in increasing muscle proteolysis, low testosterone levels in men and estrogen in women, anorexia, depression, and malnutrition [3–8]. In countries with population reference values for normal muscle mass, the classification of low muscle mass among HD patients is usually based on the comparison of results between the general population and patients, generally taking values 2 SDs below the sex-specific mean from a young reference population to define low muscle mass in HD patients [2]. In Brazil, it is more difficult to make this comparison since there is lack of data on the population. At least one Brazilian population survey addressed this issue, but the sample comprised only elderly patients,

making comparison with patients below 60 years old impossible [1]. Population data from foreign countries cannot be taken as valid for the Brazilian population.

There are several tools to assess muscle mass: computerized tomography (reliable, however with risk of radiation), magnetic resonance imaging (reliable but expensive), dual radiological absorptiometry (operator dependent), bioimpedance (reliable, safe, inexpensive) and anthropometry (biased for elderly patients) [9]. Among these tools, bioimpedance is widely used in dialysis centers, especially for nutritional evaluation and estimation of overhydration. The Body Composition Monitor (BCM®) is a device specifically designed for HD patients. It provides data on muscle mass by generating values of lean tissue index (kg/m^2). There is no valid cutoff for the lean tissue index, as assessed by BCM®, to define low muscle mass in HD patients in Brazil. It would be valuable to have simple, safe, inexpensive, objective and widely used method to determine muscle mass and detect patients at risk of low muscle mass. Screening of low muscle mass is clinically significant since low muscle mass negatively impacts quality of life and is a strong predictor of morbidity and mortality [2, 10].

Sarcopenia is a medical term which is synonymous for low muscle mass. Here we avoid referring to sarcopenia since it is currently defined by international societies not only as low muscle mass, but a combination of low muscle mass and diminished muscle strength and function [9]. Indeed, in one study muscle strength was found to be more important than low muscle mass to predict death [2]. Muscle strength can be easily assessed by hand grip testing, which has well established cutoff values to classify low muscle strength [11].

Thus, due to (i) the existence of a widely used method (bioimpedance) in dialysis centers to evaluate body composition in HD patients, (ii) the lack of a Brazilian cutoff to define low muscle mass based on bioimpedance results, and (iii) the clinical importance of muscle strength, we aimed to establish a preliminary cutoff to define low muscle mass in our patients based on muscle strength. A cutoff to define low muscle mass by bioimpedance would enable determining demographic and clinical variables associated with low muscle mass, which would be useful to identify patients at risk of low muscle mass.

First, we compared the lean tissue index, as assessed by the BCM®, between patients with low and normal muscle strength in order to determine a lean tissue index cutoff value to classify clinically important low muscle mass. Second, based on this cutoff, we looked for variables associated with low muscle mass among our patients.

Methods

Sample

Two hundred and forty-five ESRD patients formed the sample from a total of 281 patients undergoing HD in the only two dialysis centers located in the north region of Ceará state, Brazil, in October 2019. From the total of 281 patients, two were excluded because of age below 18 years old, 16 with less than three

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months of maintenance HD, 11 patients with extremity amputations precluding bioimpedance analysis, and 7 with advanced neurologic and/or rheumatologic disorders precluding hand grip testing. All patients were undergoing conventional HD (three sessions of 4 h per week) with polysulfone dialyzers (maximum number of reuses = 12).

Patient data

The demographic data, length of time on dialysis, type of vascular access and underlying etiology of ESRD were obtained from the dialysis center's medical records. The underlying renal disease was classified according to clinical criteria and not by histopathology. Classification of economic class was according to criteria of the form issued by the Brazilian Association of Research Institutes [12]. This validated instrument is used in marketing surveys and population censuses and grades economic class into five subgroups: A (best status) through E (worst status). Besides income level, its criteria include educational level of the head of household and ownership of household appliances. Each patient was assigned a low, medium or high risk index based on comorbidity, as described by Khan et al. [13]. Khan's comorbidity index takes into consideration age in three classes and nine comorbidities: diabetes, myocardial infarction, angina pectoris, congestive heart failure, liver cirrhosis, obstructive pulmonary disease, systemic collagen disease, pulmonary fibrosis and visceral malignancy. Body mass index (BMI) was calculated as kg/m^2 . Laboratory tests for serum creatinine, hemoglobin, albumin, cholesterol, calcium and phosphorus were performed. The calcium-phosphorus product was calculated by multiplying the results of calcium and phosphorus. The dose of dialysis delivered was evaluated using a second-generation Kt/V equation, as described by Daugirdas [14].

Patients' functional ability

We used the Brazilian version of the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) to assess patients' level of functional ability [15]. This instrument includes questions about usual activities like dressing, rising, eating, walking, hygiene, reaching, gripping, and about fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. HAQ-DI comprises 20 questions and generates a score from zero (no disability) to three (maximum disability).

Anthropometric measurements

All measurements were performed on the arm without fistula after the dialysis session. We assessed circumferences (mid-arm circumference, mid-arm muscle circumference, waist circumference, waist-to-hip ratio) and the sum of four skinfold sites: subscapular, suprailiac, biceps and triceps. Criteria to classify categories and normality were those well established in the literature [16].

Bioimpedance

Patients were submitted to bioimpedance analysis performed by the BCM[®] device (Fresenius Medical Care, Bad Homburg, Germany). Patients underwent bioimpedance analysis after the dialysis session. The

Loading [MathJax]/jax/output/CommonHTML/jax.js the manufacturer's manual. We obtained the following data:

lean tissue index (LTI in kg/m^2), fat tissue index (FTI in kg/m^2) and relative fluid overload (%). Overhydration was classified as relative fluid overload $> 15\%$.

Handgrip test

We used a Crown Dynamometer ® (Técnica Industrial Oswaldo Filizola) to perform three evaluations, every minute, of the hand grip strength of the dominant hand, taking as final result the mean of the three values in Kgf. During the test, patients were seated, their elbow by their side and flexed at right angles with a neutral wrist position. Cutoffs to classify normal hand grip strength were adjusted to gender and age according to Schlüssel et al. [17]

Statistical analysis

Shapiro's test was used to test the normality of the distribution of the continuous variables. Continuous variables with normal distribution are expressed as mean \pm SD and continuous variables without normal distribution as median, minimum and maximum values. Categorical variables are presented by absolute number and percentage. Comparisons were performed by the Student-*t* and Mann-Whitney tests for continuous variables, respectively, with or without normal distribution. Comparisons of frequencies were carried out by the chi-square test. Multivariate logistic regression was used to test variables as independent predictors for the presence of low muscle mass. In the multivariate analysis, variables taken as independent variables were those that differed in the bivariate comparison between patients with normal and low muscle mass. Statistical significance was considered to be a *P*-value < 0.05 . All the statistical analyses were performed using the SPSS version 22.0 program package.

Results

Sample characteristics are depicted in Table 1.

Table 1
– Sample characteristics

Variables	
Gender, n(%)	149 (60.81)
Male	96 (39.18)
Female	
Age, mean ± SD	51.3 ± 17.2
Social class, n (%)	1 (0.40)
A	18 (7.34)
B	99 (40.40)
C	105 (42.85)
D	22 (8.97)
E	
Etiology of ESRD, n (%)	81 (33.06)
Hypertension	65 (26.53)
Glomerulonephritis	42 (17.14)
Diabetes	11 (4.48)
Obstructive uropathy	10 (4.08)
Polycystic kidney disease	3 (1.22)
Lupus	33 (13.46)
Undetermined	
Time on HD, median [min-max]	24 [3–300]
Vascular access, n(%)	216 (88.16)
Fistula	29 (11.83)
Catheter	
Comorbidity index, n (%)	96 (39.18)
Low	87 (35.51)
Medium	62 (25.30)
High	
Creatinine (mg/dL), mean ± SD	7.1 ± 2.5
Hemoglobin (g/dL), mean ± SD	9.6 ± 2.5
Albumin (g/dL), mean ± SD	4.2 ± 0.6
Cholesterol (mg/dL), mean ± SD	131.9 ± 41.0
Calcium-phosphorus product (mg²/dL²), mean ± SD	44.6 ± 17.3
Kt/V, mean ± SD	2.0 ± 0.6
HAQ-DI score, median [min-max]	0.3 [0–3]
BMC (kg/m²), mean ± SD	24.4 ± 4.7
Abdominal circumference (cm), mean ± SD	91.4 ± 14.8

Variables	
Lean tissue index (kg/m ²), mean ± SD	15.4 ± 3.8
Fat tissue index (kg/m ²), mean ± SD	8.8 ± 5.5
Overhydration, n(%)	40 (16.3)
Yes	205 (83.6)
No	
Muscle strength (Kgf), mean ± SD	19.6 ± 11.2

[Table 1 is to be inserted here. Table 1 is placed at the end of the document text file]

Based on statistical difference of LTI (16.9 ± 4.0 vs. 14.9 ± 3.6 kg/m²) with a very similar SD between patients with normal and low muscle strength, we defined a cutoff of for lean tissue index higher than 15 kg/m² to classify normal muscle mass (Table 2).

Table 2 – Comparison of lean tissue index (LTI) between patients with low and normal muscle strength

	Normal muscle strength	Low muscle strength	P
LTI (kg/m ²), mean ± SD	16.9 ± 4.0	14.9 ± 3.6	< 0.001

Accordingly, there was 41.2% prevalence of low muscle mass. In the comparison between patients with normal and low muscle mass, those with low muscle mass were predominantly women, older, presented lower creatinine, higher cholesterol, more disability according to HAQ-DI score, higher fat tissue index, more prevalence of overhydration, higher risk as assessed by waist circumference, more abnormal waist-to-hip ratio, and more obesity considering the sum of four skinfold sites (Table 3).

Table 3

– Comparison of demographic and clinical variables between patients with low and normal muscle mass

Variables	Low muscle mass	Normal muscle mass	P
Gender, n(%) Male Female	39 (26.2) 62 (64.5)	110 (73.8) 34 (35.5)	< 0.001
Age, mean ± SD	54.1 ± 17.1	49.0 ± 16.9	0.012
Social class, n(%) A B C D E	0 6 (5.94) 48 (47.52) 42 (41.58) 5 (4.95)	1 (0.69) 12 (8.33) 51 (35.41) 63 (43.75) 17 (11.80)	0.165
Time on HD, median [min-max]	26 [3–300]	24 [3–216]	0.165
Vascular Access, n(%) Fistula Catheter	88 (87.12) 13 (12.87)	128 (88.88) 16 (11.11)	0.691
Comorbidity index, n(%) Low Medium High	33 (32.67) 35 (34.65) 33 (32.67)	63 (43.7) 52 (36.11) 29 (20.13)	0.061
Creatinine (mg/dL), mean ± SD	6.2 ± 2.2	7.7 ± 2.6	< 0.001
Hemoglobin (g/dl), mean ± SD	9.6 ± 1.8	9.4 ± 1.8	0.520
Albumin (g/dL), mean ± SD	4.1 ± 0.6	4.3 ± 0.6	0.194
Cholesterol (mg/dL), mean ± SD	143.1 ± 42.3	124.2 ± 38.3	< 0.001
Calcium-phosphorus product (mg²/dL²), mean ± SD	43.9 ± 16.2	45.1 ± 18.3	0.592
Kt/V, mean ± SD	1.9 ± 0.6	2.1 ± 0.6	0.054
HAQ-DI score, median [min-max]	0.6 [0–3.0]	0.2 [0-2.7]	< 0.001
BMI, mean ± SD	24.1 ± 4.5	24.6 ± 4.8	0.488
Fat tissue index, mean ± SD	11.6 ± 5.2	6.5 ± 4.6	< 0.001
Overhydration, n(%) Yes No	24 (60.0) 83(40.5)	16 (40.0) 122 (59.5)	0.045

Variables	Low muscle mass	Normal muscle mass	P
Abdominal circumference, mean ± SD	92.4 ± 13.2	91.4 ± 13.9	0.591
Mid-arm circumference, n(%)	57 (57.57)	73 (50.00)	0.255
Malnutrition	39 (39.39)	59 (40.41)	
Normal	1 (1.01)	6 (4.10)	
Overweight	2 (2.02)	8 (5.47)	
Obesity			
Mid-arm muscle circumference, n(%)	45 (46.39)	57 (38.51)	0.407
Malnutrition	52 (53.60)	91 (61.48)	
Normal			
Corrected arm muscle area, n(%)	53 (54.63)	68 (45.94)	0.271
Malnutrition	44 (45.36)	80 (54.05)	
Normal			
Waist circumference, n(%)	71 (48.63)	65 (65.65)	0.019
Normal	29 (19.86)	18 (18.18)	
Moderate	46 (31.50)	16 (16.16)	
High			
Waist to hip ratio, n(%)	72 (48.64)	69 (71.13)	0.001
Normal	76 (51.35)	28 (28.86)	
Abnormal			
Triceps skinfold, n(%)	70 (70.7)	105 (71.91)	0.792
Malnutrition	11 (11.11)	21 (14.38)	
Normal	3 (3.03)	3 (2.05)	
Overweight	15 (15.15)	17 (11.64)	
Obesity			
Sum of four skinfold sites, n(%)	3 (2.00)	2 (2.10)	0.049
Below average	30 (20.00)	20 (21.05)	
Average	49 (32.66)	48 (50.52)	
Above average	68 (45.33)	25 (26.31)	
Obesity			

[Table 3 is to be inserted here. Table 3 is placed at the end of the document text file]

After performing multivariate regressions considering low muscle mass as a dependent variable, only age, female gender, creatinine level, FTI and waist-to-hip ratio were found to be independent predictors of low muscle mass (Table 4).

Table 4 – Predictors of low muscle mass

Predictors	OR	CI 95%	P
Age	1.026	1.010–1.057	0.029
Creatinine	0.825	0.702–0.980	0.026
Cholesterol	1.007	0.987–1.023	0.116
HAQ-DI score	1.457	0.824–2.591	0.202
Gender (female)	0.153	0.073–0.359	< 0.001
Fat tissue index	0.812	0.761–0.873	< 0.001
Overhydration	1.814	0.636–5.224	0.267
Waist circumference	0.952	0.531–1.716	0.869
Waist to hip ratio	0.400	0.171–0.967	0.040
Sum of four skinfolds	0.874	0.512–1.575	0.623

Discussion

We found a very high prevalence (41.2%) of low muscle mass, similar to other studies of HD patients [2, 18]. Isoyama et al. found low muscle mass prevalence of 44% in an ongoing cohort of HD patients from Baxter Clinics [2]. Valtuille et al., studying a sample from nine HD centers in Argentina comprising 934 patients, found 58.8% prevalence of low muscle mass, as defined by low LTI [17]. It is important to highlight that our sample as well as the samples of the cited studies were formed not just of elderly patients, but with mean ages of 51.3 (our study), 53 [2] and 58 years [18]. This high prevalence of low muscle mass in a sample of relatively young patients is clinically important. Low muscle mass is a predictor of mortality with an odds ratio for death varying between 2.3 and 3.2 [10, 19]. Moreover, low muscle mass impacts quality of life, impairing the execution of daily activities (dressing, rising, eating, walking, hygiene, reaching, gripping), as we found in our sample, which was evaluated by the HAQ-DI questionnaire. The difference of the scores generated by the HAQ-DI is substantial. The maximum score is three, and the higher the score, the greater the degree of disability is. We found median of 0.2 among patients with normal muscle mass versus 0.6 in patients with low muscle mass ($p < 0.001$).

Among the variables associated with low muscle mass in our study, age was expected to be found since low muscle mass is a consequence of aging. Unlike our study, another study found that overhydration and longer time on HD were predictors of LTI [18]. We think that the lack of association between serum albumin and muscle mass has great clinical significance. Albumin is a traditional nutritional marker, widely used in the follow-up of HD patients. However, as has already been shown, serum albumin reflects muscle wasting only when its level is very low. In our sample, the mean serum albumin was 4.2 md/dL (normal value), even among patients with a high prevalence of low muscle mass. Thus, albumin is only a

marker used in ESRD was strongly associated with muscle mass: creatinine. Creatinine levels are measured monthly in dialysis centers, and in stage 5 chronic kidney disease it is useful not as a marker of renal function (as it is in earlier stages of chronic kidney disease), but as a nutritional marker, specifically associated with muscle mass. The monthly checking of serum creatinine is still the most simple and reliable way to assess muscle mass among HD patients.

Abnormal waist-to-hip ratio is a predictor of cardiovascular events in the general population. Recently, this anthropometric metric was also validated as a predictor of death and cardiovascular events among ESRD patients. Abnormal waist-to-hip ratio was found to be an independent predictor of mortality and ischemic heart disease in peritoneal dialysis patients [20]. In our study, abnormal waist-to-hip ratio was an independent predictor of low muscle mass. It is a simple and inexpensive marker that can be measured routinely as a screening tool to identify patients at risk of low muscle mass.

Our finding that FIT predicts muscle mass (in a negative correlation, the higher the FTI, the lower the LTI) calls to mind a current question related to patients undergoing HD: the so called sarcopenic obesity. Also, other results reinforce this issue in our sample: among patients with low muscle mass compared to patients with normal muscle mass, there were more obese people according to the sum of four skinfolds (45.3% vs. 26.3%; $p = 0.049$) and more patients with high risk waist circumference (31.5% vs. 16.6%; $p = 0.019$). Indeed, protein-energy wasting has been the central issue for many years in studies about nutritional status in HD patients. The pattern of protein-energy wasting as the main nutritional complication among ESRD patients is changing. In a recent study, obesity was found in 43% of HD patients and at least a portion of them presented low LTI [21]. On the other hand, protein-energy wasting was uncommon, affecting only 4% [21]. The condition of "sarcopenic obesity" among HD patients is emergent and was well detected in our study. Novel approaches for this emergent condition among ESRD patients on HD should be considered in the future.

In medical care, especially of groups of patients with chronic diseases associated with high mortality, warning markers contribute to identify patients at risk, giving an opportunity to implement targeted and individualized interventions. This fact was the main motivation for this study. Thus, interventions aiming to increase muscle mass should be tried in patients at risk, based on three aspects: diet/intake, physical activity and hormone therapy. At first glance, the increase in protein intake seems to be the simplest to measure. However, an increase in protein intake could exacerbate metabolic acidosis, and metabolic acidosis is one of the factors provoking muscle wasting. Thus, it is necessary to use supplements (amino acids) with high biological value to minimize the generation of acidosis [22]. These supplements are expensive, making their use by patients with very low economic class like ours virtually impossible. Regarding physical activity, there is evidence that resistance exercise is efficient to increase muscle mass [23]. But once again, characteristics of ESRD makes this simple remedy difficult: anemia, hypertension and renal osteodystrophy are impediments to regular exercise among HD patients. Electric stimulation and acupuncture are promising approaches that can be tried on bedridden patients, based on a study of mice [24]. Another promising approach is the use of nandrolone decanoate (an androgenic steroid). In

phase II clinical trials, this hormone was found to increase muscle mass without provoking fluid overload [25]. However, in female patients androgenic steroids could be intolerable due to the risk of virilization.

In our opinion, these interventions against muscle wasting can fail because patients undergoing HD are typically in a very advanced phase of muscle wasting. This is an important point when considering interventions. One study comprising patients not only on HD (stage 5 of chronic kidney disease), but in earlier stages (stages 3 and 4), showed a lower prevalence of low muscle mass compared to the prevalence in HD patients: 12.2% vs. 41.2% [26]. Thus, we think that interventions based on variables associated with low muscle mass, like the variables we found, should be implemented, preferably in earlier stages of chronic kidney disease. Interventions will likely be less efficient in advanced stages, when patients are already undergoing HD. Last, we should mention that our low muscle mass criterion was based on strength, and decreased strength certainly indicates advanced muscle wasting. Whether or not interventions will revert or improve muscle wasting in such advanced phases remains speculative. Prospective studies would be welcome to check if interventions to increase muscle mass can produce positive results, and mainly to verify if increased muscle mass can positively affect mortality and quality of life.

Our study has several limitations. Since the study is preliminary, trying to find a LTI cutoff to define low muscle mass, our proposed cutoff cannot be assumed to apply to other Brazilian samples. In our region, there are also fewer diabetics. Samples with more diabetics can have a different cutoff due to known effects of diabetes on muscles. Second, we assumed that LTI is equal to muscle mass because the BCM[®] device is specifically designed to distinguish muscle mass from pathologic fluid retention. However, LTI is the sum of muscle mass and fluid. To increase confidence in the BCM[®] device's results, we performed bioimpedance analysis after dialysis sessions when excess of fluid is supposed to have been removed. Nonetheless, the finding of 60% overhydration in patients with low muscle mass cannot preclude the bias of underestimating muscle mass. Even so, in multivariate analysis overhydration was not associated with muscle mass. Third, as shown by other studies, inflammatory markers could be associated with muscle mass and these were not considered in our work. However, our main intention was to study traditional and routinely used markers. Interleukin 6 and tumor necrosis factor alpha measurements are expensive and not routinely performed in dialysis centers.

Conclusions

The prevalence of low muscle mass was very high among ESRD patients undergoing HD. Older patients, women, patients with low creatinine, obese people with high FTI and those with abnormal waist-to-hip ratio should be seen as at risk. Dietary changes, encouragement of resistance exercise and the use of androgens should be considered. In our opinion, these interventions might be more efficient in earlier stages of chronic kidney disease.

List Of Abbreviations

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BCM®, The Body Composition Monitor; BMI, body mass index; ESRD, end-stage renal disease; FTI, fat tissue index; HAQ-DI, The Stanford Health Assessment Questionnaire Disability Index; HD, hemodialysis; LTI, lean tissue index.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants, and the study was approved by the ethics committee of Vale Acaraú University, with which the hospital is associated (Permit Number 65824716.7.000.5053).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors' contributions

PRS conceived and designed the study. PNG and KSO supervised the overall execution of the study. PRS, PNG and VLS analyzed and interpreted the data. PRS wrote the manuscript. All authors read and approved the final manuscript.

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