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Sarcopenia and osteoporosis in tobacco- and non-tobacco-exposure-related chronic obstructive pulmonary disease

Uma Maheswari Krishnaswamy,[1] Kavitha Venkatnarayan,[1] Rebecca Kuriyan Raj,[2] Sumithra Selvam,[3] Chitra Veluthat,[1] Priya Ramachandran,[1] Uma Devaraj[1]

[1]Department of Pulmonary Medicine, St John's National Academy of Health Sciences, Bengaluru, Karnataka; [2]Division of Nutrition, St John's National Academy of Health Sciences, Bengaluru, Karnataka; [3]Department of Biostatistics, St John's National Academy of Health Sciences, Bengaluru, Karnataka, India

Correspondence: Kavitha Venkatnarayan, Department of Pulmonary Medicine, St John's National Academy of Health Sciences, Bengaluru, Karnataka, India. E-mail: kavitha.v@stjohns.in

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Abstract

Sarcopenia and osteoporosis are important comorbidities in patients with chronic obstructive pulmonary disease (COPD). We compared the prevalence and impact of these comorbidities in tobacco-smoke-related COPD (S-COPD) and non-tobacco-smoke-related COPD (NS-COPD). The utility of rectus femoris ultrasonography as a screening tool for sarcopenia was also explored.

This cross-sectional study was conducted in a tertiary care hospital in Southern India. The COPD Assessment Test (CAT), St. George's Respiratory Questionnaire, 6-minute walk test, dual energy X-ray absorptiometry and rectus femoris ultrasonography were performed in all included participants. One hundred participants (73% S-COPD and 27% NS-COPD, respectively) were included with a mean (standard deviation - SD) age of 65.8 (8.6) years and a mean (SD) predicted forced expiratory volume at one second of 41.1% (12.6). NS-COPD participants were younger (60.7 *vs.* 67.5 years; $p<0.001$), predominantly female (88.9% *vs.* 1.4%; $p<0.001$) and had a higher body mass index (BMI) (24.8 kg/m^2 *vs.* 21.8 kg/m^2, $p=0.004$) compared to S-COPD. Sarcopenia and osteoporosis were diagnosed in 36% and 12%, respectively. Older males with S-COPD and lower BMI were sarcopenic, and the latter was an independent predictor of lower 6-minute walk distance [adjusted b = -51.4 m; 95% confidence interval (CI) = -97.0, -5.84] and higher CAT scores (adjusted b = 2.53; 95% CI = 0.21, 4.86). Rectus femoris cross-sectional area at a cut-off value of 4.34 cm^2 had 91% sensitivity and 87% negative predictive value for sarcopenia. Sarcopenia was more prevalent among older male smokers and was an independent risk factor for high symptom burden and poor exercise capacity. Rectus femoris ultrasonography is a potential screening tool for sarcopenia.

Key words: chronic obstructive pulmonary disease, sarcopenia, osteoporosis, muscle ultrasound.

Introduction

Chronic obstructive pulmonary disease (COPD) has traditionally been associated with tobacco smoking. However, with the identification of non-tobacco smoke related risk factors, it is being recognised as a disease with multiple etiotypes [1]. The Global burden of Disease study reports that tobacco smoking accounts for only a third of the global COPD burden, with most cases occurring in high income countries. The remaining two-thirds of cases have been linked to non-tobacco smoke exposures and have been mostly reported from low and middle-income countries [2]. Smoking-related COPD has been extensively studied with respect to disease progression and associated comorbid illnesses. Beyond its established role in airway inflammation and remodeling, cigarette smoke promotes systemic oxidative stress in a dose-dependent manner, potentially influencing the development and progression of COPD [3]. However, despite the significant burden, the landscape of COPD among non-tobacco related exposures remains poorly understood and the associated comorbidities are under-explored.

In addition to recognition of various etiotypes, our understanding of COPD has evolved from the latter being considered a lung-limited disease to the recognition of it being a systemic disorder with comorbidities involving diverse extrapulmonary organs [4]. Extrapulmonary manifestations of COPD have been shown to have an impact on the health-related quality of life, disease management and prognosis [5]. Thus, screening and early identification of systemic comorbidities will pave the way for comprehensive management and enhance patient outcomes. Characterisation of these comorbidities in tobacco smoke and non-tobacco smoke exposure related COPD is another area that has not been studied widely.

Sarcopenia and osteoporosis are two important extra-pulmonary manifestations which are often overlooked in patients with COPD. These comorbid conditions have been shown to significantly contribute to functional impairment apart from that attributable to impaired lung function [6].

This study was undertaken to compare the prevalence of sarcopenia and osteoporosis between tobacco smoke exposure-related COPD (S-COPD) and non-tobacco smoke exposure-related COPD (NS-COPD). Secondary objectives included evaluating the impact of sarcopenia and osteoporosis on functional status and health-related quality of life. We also assessed the diagnostic utility of rectus femoris ultrasonography as a screening tool for sarcopenia.

Materials and Methods

The study was performed in a tertiary care hospital in South India over 24 months (June 2021 to May 2023). Recruitment was done in a staggered fashion from June 2021 to March 2022 due to COVID-19 pandemic related travel restrictions. Approval was obtained from the Institutional Ethics Review Board (Study Ref No. 211/2019). Participants diagnosed with COPD according to GOLD guidelines were included in the study. Those with an exacerbation in the previous month, on long term systemic steroids, history of asthma, unstable cardiac disease and diagnosed neuromuscular diseases were excluded. Spirometry was performed using Smart PFT (Medical Equipment Europe), as per American Thoracic Society guidelines. Post-bronchodilator values were recorded after administration of 400 μg of salbutamol via metered dose inhaler with spacer.

Participants were classified into two groups based on exposure history as follows:

1. Those with at least 10 pack-years of smoking were considered as tobacco smoke exposure-related COPD (S-COPD).
2. Never-smokers with a documented history of biomass fuel exposure for at least 2 hours per day for a minimum of 10 years were classified as non-tobacco smoke exposure-related COPD (NS-COPD). Exposure to second-hand smoke was not considered in this classification.

Clinical and spirometric data of all included participants were recorded after obtaining written informed consent. Details of exacerbations, hospitalizations, and the need for domiciliary oxygen and/or non-invasive ventilatory support were also noted. Exacerbations were defined as acute worsening of respiratory symptoms requiring a change in regular medication, including emergency visits, hospitalization, or use of oral corticosteroids and/or antibiotics. Symptom burden and health-related quality of life (HRQoL) were quantified using modified Medical Research Council (mMRC) dyspnea grade, COPD assessment test (CAT) score, and St. George's Respiratory Questionnaire (SGRQ) score. Serum Vitamin D levels were measured in all participants, as its deficiency is one of the main risk factors for osteoporosis and sarcopenia.

Physical performance was assessed using the Short Physical Performance Battery (SPPB), which included gait speed assessment, chair stand test, and balance testing. A whole-body dual energy X-ray absorptiometry (DXA- Lunar Prodigy Advanced whole-body scanner GE Medical Systems, software version 12.30) scan was performed to measure fat mass, lean mass, and bone mineral density. Hand grip strength was assessed using a hand dynamometer (Camry 200 lbs digital hand dynamometer). Sarcopenia was defined as appendicular skeletal muscle mass index (ASMI = ASM/height^2) of <7.0 kg/m^2 for men and <5.5 kg/m^2 for women and a handgrip strength of <26 kg for men and <18 kg for women or a gait speed of 0.8m/s [7,8]. Osteoporosis and osteopenia were defined as per WHO classification using T score (-1 to -2.5 defined as osteopenia and -2.5 as osteoporosis). Fracture risk assessed using Fracture risk assessment (FRAX) score.

Ultrasonographic evaluation of rectus femoris and diaphragm was performed using SonoSite S-ICU machine. The procedure followed is described below.

Rectus femoris ultrasonography: Rectus femoris cross-sectional area (RF-CSA), muscle thickness and circumference were measured by positioning the linear probe between the upper 2/3 and lower 1/3 of the distance between anterior superior iliac spine and upper border of the patella. An average of 3 readings were documented for all the above measurements.

Diaphragm ultrasonography: With the participant in semi-recumbent (30-45°) position, diaphragmatic excursions were measured using the curvilinear transducer (4 MHz) placed in a craniocaudal orientation below the costal margin at the mid-clavicular line. Using M mode, real-time movement of the diaphragm was recorded using the liver as the window. The linear transducer (10-15 MHz) was then placed at the anterior axillary line between the seventh and ninth ribs, and diaphragm was identified in the zone of apposition. Diaphragm thickness was measured at the end of inspiration and end of expiration. Diaphragmatic thickening fraction (DTF) was calculated as a percentage using the following formula:

DTF = [(Thickness at end inspiration – Thickness at end expiration)/ Thickness at end expiration].

With an expected prevalence of 21% for sarcopenia, the minimum sample size required was 99 participants with a 95% confidence and a margin of error of 8%. A higher margin of error was acceptable as the gold standard investigation (DEXA scans) were used to ascertain sarcopenia.

Statistical analysis

Data was collected and managed on Microsoft Excel spreadsheet. Normality of variables was assessed using Q-Q plot. Descriptive statistics were reported as mean (SD) or median (IQR) for continuous data and frequency and percentages for categorical data. Comparison of variables between groups was done using Chi square test for categorical and independent t-test or Mann-Whitney U test as appropriate for continuous variables. Multiple linear regression analysis was performed to evaluate the association between sarcopenia, HRQoL and muscle ultrasound parameters. Regression coefficients were adjusted for age, sex, and body mass index (BMI).

Pearson correlation co-efficient was calculated to evaluate the strength of association between rectus femoris ultrasonographic parameters and muscle mass evaluated on DEXA scan. Receiver- operating-characteristic (ROC) curves were constructed to arrive at a cut-off value for rectus femoris ultrasonographic parameters to diagnose sarcopenia. Sensitivity, specificity, positive predictive, and negative predictive values were reported. All analyses were performed using SPSS Version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered as $p < 0.05$.

Results

One hundred COPD participants were included in the study, of which 73 were S-COPD and 27 were NS-COPD. The mean (SD) age of the study population was 65.8 (8.6) years with a male predominance (75%). The mean (SD) percentage predicted FEV1 was 41.1% (12.6). Systemic hypertension (27%) and diabetes mellitus (20%) were the commonly reported co-morbidities. Baseline characteristics of the study population are summarized in Table 1.

Comparison of characteristics of S-COPD and NS-COPD

Participants with NS-COPD were significantly younger, comprised of females, and had a higher BMI than those with S-COPD. There was no significant difference in the exacerbation rates, co-morbidities, severity of airflow limitation, exercise capacity, SGRQ, or CAT scores between the two sub-groups.

Diaphragm excursion was higher in S-COPD with sniff excursion being significantly higher than NS-COPD. Rectus femoris circumference, area, and thickness were significantly higher in S-COPD. Vitamin D levels were not significantly different between the 2 groups. The comparison of characteristics between the two groups is summarized in Table 2.

Assessment for sarcopenia and osteoporosis

Sarcopenia was diagnosed in 36% of the study population. Participants with sarcopenia were significantly older, predominantly males, had a lower BMI and belonged to the S-COPD sub-group. They also had a lower six-minute walk distance, higher SGRQ scores in the symptom and activity domains as well as higher CAT scores (Table 3).

Ultrasonography of rectus femoris showed significantly lower RF-CSA and thickness in participants with sarcopenia. Both RF-CSA and thickness had a significant positive correlation with the appendicular skeletal muscle index derived from the DEXA scan ($r=0.382$ and 0.386 respectively; $p<0.001$). On evaluating the diagnostic performance of RF ultrasound for sarcopenia, RF-CSA at a cut-off value of 4.34 cm^2 had a sensitivity of 0.91 and a specificity of 0.31; RF thickness at a cut-off value of 0.73 had a sensitivity of 0.52 and specificity of 0.78 (Table 4, Figure 1).

Multivariate regression analysis showed that age was the only independent risk factor for the development of sarcopenia. After adjusting for age, sex, and BMI, presence of sarcopenia was an independent predictor of a lower six-minute walk distance, a higher CAT score and lower rectus femoris thickness and CSA (Table 5).

Osteopenia and osteoporosis were diagnosed in 51% and 12% of participants, respectively. Participants with osteopenia had a significantly higher FRAX score and lower ASMI in comparison to those without osteopenia. There were no significant differences between the osteopenic and non-osteopenic participants with respect to demographic features, severity of airflow limitation, HRQoL scores, Vitamin D levels, or muscle assessment (Table 3).

Discussion

This study attempted to characterise and compare the clinical profile, functional status, diaphragm function, sarcopenia and osteoporosis among tobacco smoke related and non-tobacco smoke exposure related COPD. Despite its high burden, our understanding of COPD in non-tobacco smoke exposed remains limited. This subset of COPD has been reported in females, who are younger, have a higher body mass index and experience a slower decline in lung functions [2]. However, they have been shown to exhibit higher exacerbation rates and health care utilization [9]. Our study also found that NS-COPD group was younger, female predominant and had a higher BMI. But, unlike earlier studies, we did not find any difference in the number of exacerbations between the two groups. This may have been due to the inherent design of our study, wherein disease profiling, assessment of functional status, bone, and muscle health, were performed in COPD participants visiting the out-patient department. It may also be due to under-reporting of disease exacerbations by participants.

We found that diaphragm excursion, RF CSA, thickness, and circumference were higher in S-COPD. This finding was probably because of male preponderance in the S-COPD sub-group. After adjusting for gender in multivariate analysis, the difference between groups was no longer statistically significant, suggesting that gender distribution rather than exposure status accounted for the observed difference. Earlier studies have also reported that smoking has no significant effect on diaphragm excursion on comparing healthy smokers and non-smokers [10,11].

COPD encompasses a complex interplay of shared risk factors and systemic inflammation, leading to a state of multimorbidity. Sarcopenia and osteoporosis are important, under-recognised extrapulmonary manifestations which can contribute to the functional impairment in these patients. Prevalence of sarcopenia in patients with COPD varies widely with an aggregate estimate of 21% in hospital-based population [12]. We found a prevalence of 36% in our study population. This may be due to recruitment of participants with more severe COPD as ours is a tertiary care and referral hospital. Although systemic inflammatory response has been found to be an important contributor to sarcopenia, the association of smoking with sarcopenia has yielded conflicting results [13-15]. We found that participants with sarcopenia were more likely to be smokers. Sarcopenia has been reported to be associated with disease severity, severity of dyspnea, and exercise capacity [16]. We did not find any difference in the severity of airflow limitation, those with sarcopenia had poorer symptom and activity domain scores on SGRQ and worse CAT scores compared to those without sarcopenia. They also had a lower 6-minute walk distance, signifying poorer exercise capacity. All these findings highlight the fact that sarcopenia can increase symptom burden and have a negative impact on HRQoL in COPD. Thus, it may be important to routinely screen all patients with COPD for sarcopenia and plan targeted interventions to improve muscle mass and activity.

The diagnosis of sarcopenia is traditionally based on quantification of muscle mass using computed tomography, magnetic resonance imaging or DEXA scans [17]. However, these modalities have limited accessibility, are expensive and may pose a risk of radiation exposure, especially when periodic assessments are required. Ultrasonography, on the other hand, is non-invasive, inexpensive and radiation-free. Besides, its availability as a point-of-care device makes it an ideal modality for longitudinal muscle assessment. However, the utility of rectus femoris ultrasound in diagnosing sarcopenia as well as the optimal cut-off values are yet to be established and validated [18].

In our study, RF-CSA and thickness had a significant correlation with ASMI. In addition, it had a high sensitivity (0.91) and negative predictive value (0.87) which indicates a potential to serve as a screening tool in settings where other imaging modalities may not be easily available. Similar prevalence and impact of sarcopenia have been reported by Deng et al, who derived a RF thickness cut-off of 5.2cm (sensitivity 76.3%, specificity 75%) and RF CSA cut-off of 6.8cm^2 (sensitivity 90.9%, specificity 67.8%) in a Chinese population [19]. Further studies are required to validate these cut-offs in different populations of COPD including the entire spectrum of disease severity.

COPD related osteoporosis is also postulated to be secondary to the systemic inflammatory state with a prevalence of 38%. Lower BMI decreased fat-free mass, and presence of sarcopenia were significant risk factors for osteoporosis reported in a systematic review by Chen et al [20]. We found a lower prevalence of osteoporosis (12%) in our study. In addition, our study also showed that sarcopenia was associated with osteopenia.

Our study has a few limitations. It is a single-centre study, and similar results need to be demonstrated in a bigger sample of COPD patients for generalizability. As this was a hospital-based study, participants across the severity spectrum of COPD could not be recruited. There was a numerical imbalance between the S-COPD and NS-COPD groups, which may limit the statistical power to detect differences between the groups. As a result, we did not have a significant representation of female smoker and male non-smoker COPD, which could have helped understand the NS-COPD subtype better. Additional factors contributing to sarcopenia, like nutrition, steroid use, and activity levels were not assessed. The cut-offs obtained for rectus femoris ultrasound parameters would also need to be validated in a larger set of patients. The cross-sectional design precludes inference of causal relationships between sarcopenia and clinical outcomes.

Conclusions

Participants with NS-COPD were younger, exhibited a female preponderance and had a higher BMI when compared to those with S-COPD. Sarcopenia was more prevalent among older, male smokers with a lower BMI. The presence of sarcopenia was an independent risk factor for poorer exercise capacity and higher symptom burden. Rectus femoris ultrasound could serve as a potential screening tool for sarcopenia.

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Table 1. Baseline characteristics of participants with COPD.

Characteristics (N=100)	Values
Age (yrs) [Mean (SD)]	65.8 (8.6)
Males (%)	75
Smokers (%)	73
Smoking index [Mean (SD)]	1000 (412)
Biomass exposure (%)	27
Biomass index [Median (IQR)]	110 (80, 160)
Duration of symptoms (yrs) [Mean (SD)]	6.79 (3.6)
Number of exacerbations [Median (IQR)]	2 (1, 3)
BMI (kg/m^2) [Mean (SD)]	22.6 (4.6)
Long Term Oxygen Therapy (%)	6
FEV1/ FVC [Mean (SD)]	56.6 (9.1)
FEV1 (liters) [Mean (SD)]	0.9 (0.3)
FEV1% predicted [Mean (SD)]	41.1 (12.6)
Six-minute Walk distance (m) [Mean (SD)]	395 (101)
Co-morbidities (%)	
Systemic Hypertension	27
Diabetes Mellitus	20
Vitamin D3 levels (ng/mL) [Mean (SD)]	20.8 (8.2)

Table 2. Comparison of demographic and comorbidity profile between S-COPD and NS-COPD.

Parameter	Total (n=100)	S-COPD (n=73)	NS-COPD (n=27)	p
Age (yrs)	65.8 (8.6)	67.5 (7.8)	60.9 (8.8)	**<0.001**
Males [n (%)]	75 (75)	72 (98.6)	3 (11.1)	**<0.001**
BMI (kg/m^2)	22.6 (4.6)	21.8 (4.2)	24.8 (4.9)	**0.004**
Number of exacerbations [Median (IQR)]	1 (0, 3)	1 (0, 1)	1 (0, 1)	0.199
Systemic Hypertension [n (%)]	27 (27)	20 (27.3)	7 (25.9)	0.883
Diabetes Mellitus [n (%)]	20 (20)	16 (21.9)	4 (14.8)	0.43
mMRC grade [Median (IQR)]	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.65
FEV1 (% predicted)	41.1 (12.6)	39.8 (12.3)	44.5 (13)	0.152
Six-minute Walk distance (m)	395 (101)	403 (103)	373 (95)	0.219
SGRQ total score	44.7 (16.3)	43.4 (15.2)	47.9 (18.8)	0.293
SGRQ symptom score	58.1 (15.3)	57.3 (15.6)	60.1 (14.3)	0.497
SGRQ activity score	62.2 (16.6)	61.3 (15.6)	64.5 (18.9)	0.531
SGRQ impacts score	30.2 (18.8)	28.7 (17.4)	34.0 (22)	0.326
CAT score	17.3 (5.6)	16.9 (5.5)	18.3 (5.9)	0.204
FRAX* score -hip fracture	2 (4.2)	1.6 (1.6)	3.1 (7.6)	0.265
FRAX* score - major osteoporotic fracture	6.8 (5.8)	5.9 (3.0)	9.41 (9.7)	**0.018**
Diaphragm assessment				
1. Excursion (cm)				
a. Tidal breathing	1.95 (0.8)	2.04 (0.9)	1.68 (0.6)	0.079
b. Deep breathing	4.45 (1.4)	4.63 (1.57)	3.9 (1.08)	0.06
c. Sniff	3.04 (1.2)	3.21 (1.3)	2.5 (0.67)	**0.037**
2. Thickening fraction in tidal breathing (%)	44.7 (26.4)	45.1 (25.6)	43.8 (28.8)	0.46
Rectus Femoris (RF) assessment				
1. RF circumference (cm)	9.55 (1.3)	9.8 (1.3)	8.6 (1.0)	**<0.001**
2. RF-CSA (cm^2)	3.59 (1.3)	3.83 (1.3)	2.91 (0.8)	**0.001**
3. RF thickness (cm)	0.89 (0.2)	0.93 (0.29)	0.79 (0.2)	**0.025**
T score	-1.14 (1.2)	-1.0 (1.1)	-1.4 (1.4)	0.21
ASMI** (kg/m^2)	6.04 (0.8)	6.07 (0.8)	5.93 (0.9)	0.44
Vitamin D3 levels (ng/mL)	20.8 (8.2)	20.6 (10)	21.3 (5.9)	0.655

All values have been expressed as mean (SD) unless otherwise specified; t test/ Mann-Whitney U applied for between group comparison; Chi-square test has been applied for between group comparison. * - Fracture risk assessment score, ** - Appendicular Skeletal Muscle Mass index

Table 3. Comparison of characteristics between sarcopenic and osteopenic patients.

Parameter	Sarcopenic (n=36)	Non-sarcopenic (n=64)	p	Osteopenic (n=51)	Non-osteopenic (n=49)	p
Age (yrs)	69.5 (7.7)	63.6 (8.4)	**0.001**	66.5 (7.9)	64.9 (9.2)	0.353
Males [n (%)]	32 (88.8)	43 (67.1)	**0.016**	35 (68.6)	40 (81.6)	0.133
Smokers [n (%)]	31 (86.1)	42 (65.6)	**0.027**	35 (68.6)	38 (77.5)	0.315
BMI (kg/m^2)	21.4 (3.7)	23.2 (4.9)	**0.047**	21.8 (4.7)	23.4 (4.3)	0.054
FEV1 % predicted (%)	39.2 (13.8)	42.1 (11.9)	0.280	40.4 (11.7)	41.7 (13.6)	0.614
6-minute walk distance (m)	366 (114.4)	409.7 (91.2)	**0.047**	394.1 (98.2)	395.6 (105.2)	0.748
SGRQ total score	48.7 (16)	42.4 (16.1)	0.064	46.4 (17.1)	43.5 (15.4)	0.404
SGRQ symptom score	62.1 (14.1)	55.8 (15.6)	**0.049**	58.6 (14.8)	57.4 (15.9)	0.693
SGRQ activity score	66.6 (17.1)	59.7 (15.8)	**0.047**	63.8 (16.1)	60.5 (16.9)	0.389
SGRQ impacts score	34.5 (18.6)	27.7 (18.6)	0.083	32.1 (20.1)	28.1 (17.2)	0.508
CAT score	18.9 (5.2)	16.4 (5.6)	**0.033**	17.1 (5.3)	17.4 (5.9)	0.438
FRAX* score (hip fracture)	2.03 (1.8)	2.08 (5.1)	0.952	3.5 (5.5)	0.5 (0.4)	**<0.001**
FRAX* score (major osteoporotic fracture)	6.6 (3.0)	7.0 (6.9)	0.793	9.4 (7.2)	4.2 (1.4)	**<0.001**
Diaphragm assessment						
1. Excursion (cm)						
a. Tidal breathing	1.91 (0.75)	1.97 (0.91)	0.757	1.7 (0.7)	2.1 (0.9)	0.096
b. Deep breathing	4.35 (1.41)	4.5 (1.53)	0.634	4.2 (1.5)	4.6 (1.4)	0.170
c. Sniff	3.02 (1.23)	3.05 (1.19)	0.897	2.9 (1.1)	3.1 (1.2)	0.370
2. Thickening fraction in tidal breathing (%)	47.9 (29.6)	42.8 (24.3)	0.356	45.2 (29.8)	44.1 (22.4)	0.579
Rectus Femoris (RF) assessment						
1. RF circumference (cm)	9.39 (0.95)	9.64 (1.56)	0.317	9.6 (1.5)	9.4 (1.1)	0.754
2. RF CSA (cm2)	3.18 (0.92)	3.81 (1.44)	**0.010**	3.5 (1.4)	3.5 (1.1)	0.497
3. RF thickness (cm)	0.79 (0.3)	0.95 (0.25)	**0.007**	0.8 (0.2)	0.9 (0.2)	0.618
ASMI** (kg/m^2)	5.71 (0.65)	6.22 (0.9)	**0.002**	5.7 (0.7)	6.3 (0.8)	**<0.001**
SPPB# score	6.5 (2.5)	7.7 (2.3)	**0.016**	7.1 (2.5)	7.5 (2.3)	0.405
Gait speed (m/s)	0.9 (0.4)	1.1 (0.3)	**<0.001**	1.0 (0.5)	1.1 (0.3)	0.148
Handgrip (kg)	22.2 (4.1)	26.8 (6.3)	**0.011**	24.1 (5.9)	27.2 (5.9)	**0.011**
Vitamin D3 levels (ng/ml)	21.6 (8.3)	20.3 (8.2)	0.443	20.2 (10.0)	21.4 (5.9)	0.062

All values have been expressed as mean (SD); t test/ Mann-Whitney U applied for between group comparison Chi-square test has been applied for between group comparison. * - Fracture risk assessment score, ** - Appendicular Skeletal Muscle Mass index. # - Short Physical Performance Battery

Table 4. Diagnostic performance metrics of Rectus Femoris (RF) Ultrasonography (USG) for sarcopenia.

USG parameter	Cut-off value	AUC	Sensitivity	Specificity	PPV	NPV
RF circumference	10	0.53	0.83	0.37	0.42	0.80
RF CSA	4.34	0.62	0.91	0.31	0.42	0.87
RF thickness	0.73	0.68	0.52	0.78	0.57	0.74

Table 5. Multiple linear regression on the association between clinical parameters with sarcopenia status.

Parameter	Sarcopenic (n=36)	Non-sarcopenic (n=64)	Unadjusted regression coefficient	Adjusted regression coefficient*
Six-minute Walk distance(m)	366 (114.4)	409.7 (91.2)	**-43.7 (-86.8, -0.62)**	**-51.4 (-97.0, -5.84)**
SGRQ total score	48.7 (16)	42.4 (16.1)	6.30 (-0.36, 12.9)	5.59 (-1.21, 12.4)
SGRQ symptom score	62.1 (14.1)	55.8 (15.6)	6.26 (0.02, 12.5)	5.38 (-1.20, 11.9)
SGRQ activity score	66.6 (17.1)	59.7 (15.8)	6.84 (0.11, 13.5)	6.31 (-0.70, 13.3)
SGRQ impacts score	34.5 (18.6)	27.7 (18.6)	6.79 (-0.91, 14.5)	5.95 (-1.86, 13.7)
CAT score	18.9 (5.2)	16.4 (5.6)	**2.49 (0.20, 4.78)**	**2.53 (0.21, 4.86)**
Diaphragm assessment				
1. Excursion (cm)				
a. Tidal breathing	1.91 (0.75)	1.97 (0.91)	-0.06 (-0.41, 0.30)	-0.24 (-0.57, 0.10)
b. Deep breathing	4.35 (1.41)	4.5 (1.53)	-0.15 (-0.76, 0.46)	-0.37 (-0.97, 0.22)
c. Sniff	3.02 (1.23)	3.05 (1.19)	-0.03(-0.53, 0.46)	-0.23 (-0.71, 0.23)
2. Thickening fraction during tidal breathing (%)	47.9 (29.6)	42.8 (24.3)	5.09 (-5.80, 16.0)	2.47 (-9.36, 14.3)
Rectus Femoris (RF) assessment				
1. RF circumference (cm)	9.39 (0.95)	9.64 (1.56)	-0.25(-0.83, 0.32)	-0.37 (-0.94, 0.18)
2. RF CSA (cm^2)	3.18 (0.92)	3.81 (1.44)	**- 0.62 (-1.16, -0.09)**	**- 0.65 (-1.17, -0.13)**
3. RF thickness (cm)	0.79 (0.3)	0.95 (0.25)	**- 0.15 (-0.26, -0.04)**	**- 0.15 (-0.26, -0.03)**

**- Regression coefficient adjusted for age, sex and BMI*

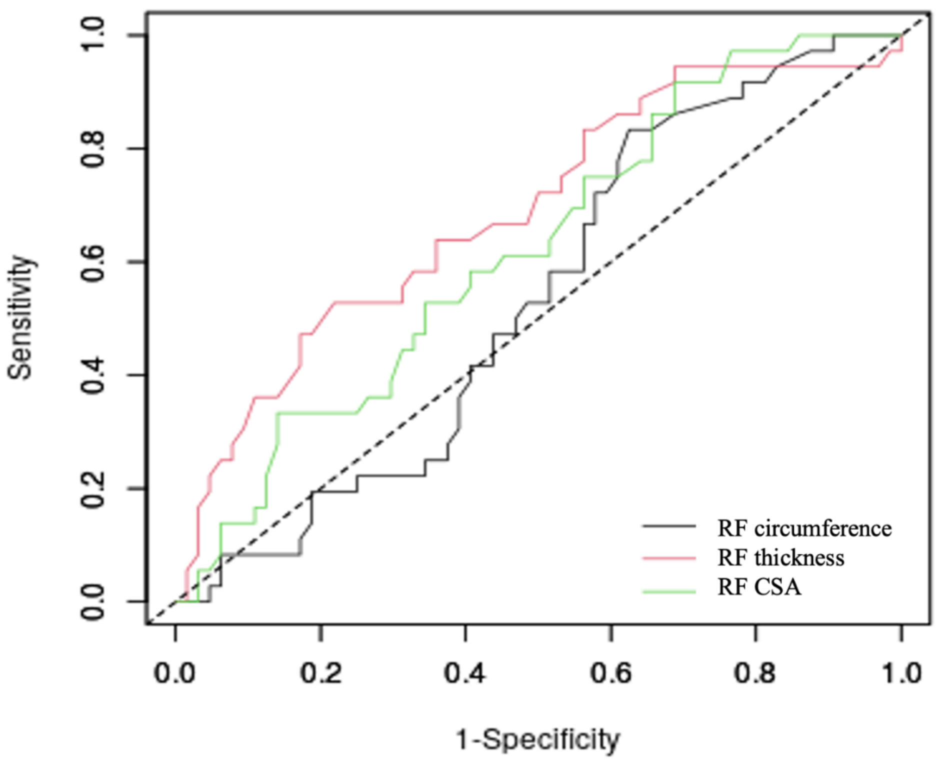

Figure 1. Receiver operating characteristic curve for diagnostic utility of rectus femoris ultrasound for sarcopenia.