Sarcopenia in COPD patients: Prevalence, patients’ characteristics and predictive factors

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ABSTRACT
INTRODUCTION Taking into consideration multifactorial origin of sarcopenia and extrapulmonary manifestations of chronic obstructive pulmonary disease (COPD), our study aimed to determine the prevalence and predictive factors for sarcopenia among COPD patients.

METHODS We examined 190 patients with COPD in Ukraine and Poland using bioelectric impedance analysis, hand-grip dynamometry, 6MWT and several questionnaires to assess clinical characteristics of the patients.

RESULTS Sarcopenia was detected in 25.3% of all patients with COPD. There was a significant difference between patients with and without sarcopenia in age, acute exacerbations of COPD, CAT, FEV₁, BODE and CCI, Borg scope (post 6MWT), hand-grip strength, BMI, fat mass index, level of visceral fat, fat percentage, skeletal muscle index, gait speed, and 6MWT distance. According to regression analysis, factors related to sarcopenia were body mass index, visceral fat level, daily physical activity, percentage of fat and GOLD 3 airflow limitation.

CONCLUSIONS Sarcopenia affected almost every fourth COPD patient and was associated with low BMI, high level of visceral fat and percentage of body fat, limited physical activity, and severe airflow limitation.

INTRODUCTION Chronic obstructive pulmonary disease (COPD) as a systemic disease is usually present with numerous comorbidities. One of the most common overlapping diseases is a skeletal muscle dysfunction. According to the GOLD 2020 Report, skeletal muscle dysfunction is characterized by loss of muscle cells and dysfunction of the remaining cells1. This definition is similar to the definition of the sarcopenia from the latest revision of European Working Group on Sarcopenia in Older People (EWGSOP2), according to which sarcopenia should be defined as low muscle strength combined with low muscle quantity or quality2. EWGSOP2 highlighted the role of sarcopenia as an important factor responsible for the impairment of daily physical activity, development of the cardiometabolic syndrome, and other complications. Presence of sarcopenia should be considered as being associated with an overall mortality and COPD-related mortality risk factor3, increased length of hospital stay, risk for hospitalization, lower probability of being discharged home4 and independently increasing hospital costs at hospital admission from 34% to 58.5% depending on the age of the population5. According to Goates et al.6, sarcopenia results in a great economic burden on the US healthcare system with total costs of hospitalizations amounting to more than US$ 19 billion6.

Development of sarcopenia is a multifactorial process. EWGSOP2 determined factors that are related to the development of primary or secondary sarcopenia. According to EWGSOP2, the main cause for primary sarcopenia is ageing2. Secondary sarcopenia is caused by such factors as diseases, inactivity, and poor nutrition. But the structure of predictive factors for sarcopenia among patients with COPD is still not clear. Taking into account an increase in systemic inflammation during an acute exacerbation, extrapulmonary manifestations and comorbidities, and progressive airflow limitation, may result in physical inactivity and other comorbidities acting as separate factors for sarcopenia5.

Our study aimed to determine the prevalence and predictive factors of sarcopenia development in COPD.
METHODS
This study complied with the Declaration of Helsinki and received permission from the local ethics committees of the National Pirogov Memorial Medical University, Vinnytsya, Ukraine (No. 9 01.11.2018) and Medical University of Silesia, Katowice, Poland (PCM/0022/KB1/53/19). All recruited participants had confirmed COPD diagnosis based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and filled in an informed consent form. Patients with acute exacerbation of COPD and subjects who suffered from conditions that result in an inability to participate in research (disabling disorders of the musculoskeletal system, severe neurologic, cognitive and psychiatric disease, severe pulmonary hypertension, unstable cardiovascular disease, etc.) were excluded from the study.

In all, 190 COPD patients were recruited for the study (172 in Ukraine, 18 in Poland). They were classified according to GOLD guidelines into the following groups: A 1.6% (3 patients), B 37.4% (71 patients), C 38.4% (73 patients), and D 22.6% (43 patients).

All participants underwent a bioelectric impedance analysis to assess muscle quantity according to the percentage of muscle tissue in the body, fat-free mass index (FFMI) and skeletal muscle index (SMI). Additionally, we measured body mass index (BMI) and fat mass index (FMI) for each person. Skeletal muscle strength was assessed using hand-grip dynamometry of the dominant hand, and physical performance using gait speed by 6-minute walk test (6MWT). Charlson Comorbidity Index (CCI) has been used as an effective tool to categorize comorbid conditions and to evaluate mortality risk. Quality of life was evaluated using St. George’s respiratory questionnaire (SGRQ) with further calculation of three components: symptoms (effect of respiratory symptoms, their frequency and severity), activity (activity limitation caused by breathlessness), and impact (social and psychological disturbances resulting from airways disease).

Symptoms of the disease were evaluated using the COPD assessment test (CAT) and mMRC (Modified Medical Research Council) Dyspnea Scale.

EWGSOP2 criteria were used to diagnose sarcopenia. Sarcopenia was confirmed by documentation of low muscle strength and low muscle quantity. Additional documentation of low muscle performance was considered severe sarcopenia. The cut-off points for decreased skeletal muscle strength were hand-grip strength <27 kg for men and <16 kg for women, for decreased physical performance gait speed ≤0.8 m/s, for low muscle quantity SMI <7.0 kg/m² for men and <5.5 kg/m² for women.

Statistical analysis
Our primary data and results are expressed as either mean ± SD or frequency and percentage. Kolmogorov-Smirnov test was used to assess the normality of data distribution. Man-Whitney test and Independent Samples T-test was used to compare numerical parameters between patients with and without sarcopenia. Categorical variables (gender and comorbidity categories) were compared using Pearson’s chi-squared test between patients with and without sarcopenia. Binomial logistic regression analysis was applied to assess predictors for sarcopenia. A value of p<0.05 was considered statistically significant. SPSS Statistics 20.0 software package was used to perform all analyses.

RESULTS
Prevalence of sarcopenia among COPD patients is highlighted in Figure 1. We found that according to EWGSOP2 criteria, sarcopenia was present in 25.3% (48 persons) of all COPD patients. It was present in 26.7% of males (46 patients) and 11.1% of females (2 patients). Severe sarcopenia was found in 6.3% of all patients (12 persons). All patients with severe sarcopenia were male.

Description of the demographic, clinical and body composition features of examined persons are presented in Table 1. COPD patients with sarcopenia were significantly older compared to COPD without sarcopenia (72.9±9.7 years opposed to 70.2±8.4 years, p<0.05). Patients with sarcopenia had significantly higher body mass index (BMI) and fat mass index (FMI) compared to patients without sarcopenia. Additionally, hand-grip strength was significantly lower in patients with sarcopenia (22.3±9.1 kg) compared to patients without sarcopenia (25.4±9.6 kg). Severe sarcopenia was associated with significantly lower hand-grip strength (14.8±5.7 kg) compared to patients with mild sarcopenia (23.6±9.3 kg). Patients with severe sarcopenia had significantly lower gait speed (0.7±0.2 m/s) compared to patients with mild sarcopenia (0.9±0.2 m/s).

Figure 1. Prevalence of sarcopenia among COPD patients
Table 1. Demographic, clinical characteristics and body composition of the patients (N=190)

|                                | All patients | With sarcopenia (n=48) | Without sarcopenia (n=142) | p       |
|--------------------------------|--------------|------------------------|-----------------------------|---------|
| **Gender**                     |              |                        |                             |         |
| Males                          | 172 (90.5)   | 46 (95.8)*             | 126 (88.7)                  | <0.001  |
| Females                        | 18 (9.5)     | 2 (4.2)*               | 16 (11.3)                   | <0.001  |
| **Age (years)**                |              |                        |                             |         |
| Total                          | 66.1±10.5    | 72.9±9.7*              | 63.8±9.8                    | <0.001  |
| Males                          | 65.8±10.5    | 72.9±9.9*              | 63.2±9.5                    | <0.001  |
| Females                        | 68.6±10.7    | 71.5±2.1               | 68.2±11.3                   | 0.471   |
| **Clinical characteristics**   |              |                        |                             |         |
| Duration of COPD (years)       | 5.2±3.1      | 5.6±3.0                | 5.0±3.2                     | 0.251   |
| Smoking history (pack-years)   | 36.4±21.0    | 38.3±21.3              | 35.7±21.0                   | 0.454   |
| Acute exacerbation of COPD (per year) | 1.92±1.6    | 2.4±1.3*               | 1.8±1.7                     | 0.001   |
| CAT                            | 18.1±7.4     | 21.2±6.3*              | 17.0±7.5                    | 0.001   |
| mMRC                           | 2.45±1.1     | 2.7±1.0                | 2.4±1.1                     | 0.184   |
| FEV1 (% predicted)             | 45.7±17.5    | 40.0±17.0*             | 47.7±17.3                   | 0.008   |
| BODE index                     | 4.0±2.6      | 5.7±2.6*               | 3.5±2.3                     | <0.001  |
| CCI                            | 2.6±1.4      | 3.3±1.3*               | 2.3±1.3                     | <0.001  |
| Myocardial infarction          | 8 (4.2)      | 2 (4.2)                | 6 (4.2)                     | 0.986   |
| Congestive heart failure       | 35 (18.4)    | 13 (27.1)              | 22 (15.5)                   | 0.074   |
| Peripheral vascular disease    | 7 (3.7)      | 3 (6.3)                | 4 (2.8)                     | 0.277   |
| Cerebrovascular accident or transient ischemic attack | 5 (2.6)    | 1 (2.1)                | 4 (2.8)                     | 0.785   |
| Connective tissue disease      | 3 (1.6)      | 1 (2.1)                | 2 (1.4)                     | 0.747   |
| Peptic ulcer disease           | 5 (2.6)      | 2 (4.2)                | 3 (2.1)                     | 0.445   |
| Uncomplicated diabetes         | 17 (9.0)     | 6 (12.5)               | 11 (7.7)                    | 0.321   |
| Diabetes with end-organ damage | 8 (4.2)      | 2 (4.2)                | 6 (4.2)                     | 0.986   |
| Moderate to severe chronic kidney disease | 4 (2.1) | 1 (2.1) | 3 (2.1) | 0.990 |
| Localized solid tumor          | 3 (1.6)      | 1 (2.1)                | 2 (1.4)                     | 0.747   |
| Heart rate (pre 6MWT) (bpm)    | 82.5±10.4    | 75.0±9.8               | 83.0±10.6                   | 0.474   |
| Heart rate (post 6MWT) (bpm)   | 97.4±9.9     | 90.2±9.8               | 97.9±10.1                   | 0.460   |
| SaO2 (pre 6MWT) (%)            | 92.2±3.3     | 93.1±3.2               | 92.2±3.4                    | 0.821   |
| SaO2 (post 6MWT) (%)           | 86.8±7.2     | 90.3±7.0               | 86.6±7.4                    | 0.665   |
| Borg score (pre 6MWT)          | 1.3±1.3      | 2.1±1.4                | 1.2±1.2                     | 0.068   |
| Borg score (post 6MWT)         | 4.6±2.8      | 6.7±3.3*               | 4.1±2.4                     | 0.021   |
| SGRQ Symptoms                  | 69.4±15.3    | 73.6±11.5*             | 68.0±16.1                   | <0.001  |
| SGRQ Activity                  | 66.1±20.7    | 76.4±14.6*             | 62.7±21.3                   | 0.028   |
| SGRQ Impact                    | 48.3±17.8    | 57.1±15.1*             | 45.3±17.7                   | <0.001  |
| SGRQ Total                     | 57.3±16.2    | 65.4±12.4*             | 54.6±16.4                   | <0.001  |
| **BMI (kg/m²)**                |              |                        |                             |         |
| Males                          | 26.8±6.6     | 23.2±5.7*              | 28.1±6.4                    | <0.001  |
| Females                        | 28.6±7.9     | 27.8±17.3              | 28.7±7.1                    | 0.889   |
| **Hand-grip strength (kg)**    |              |                        |                             |         |
| Males                          | 33.1±12.0    | 21.3±5.3*              | 37.2±10.8                   | <0.001  |
| Females                        | 17.5±5.2     | 12.5±3.5               | 18.1±5.1                    | 0.155   |

Continued
vs 63.8±9.8 years, p<0.001). COPD patients with sarcopenia had significantly more exacerbation in the last year compared to patients without sarcopenia (2.4±1.3 vs 1.8±1.7, p=0.001) but the difference was not significant when an mMRC scale was used. COPD sarcopenia patients had a significantly lower FEV₁ compared to the control subjects (40.0±17.0% of pred. vs 47.7±17.3% of pred., p=0.008). Moreover, COPD patients with sarcopenia had a significantly worse quality of life according to all components of SGRQ: symptoms (73.6±11.5 vs 68.0±16.1, p<0.001), activity (76.4±14.6 vs 62.7±21.3, p=0.028), impact (57.1±15.1 vs 45.3±17.7, p<0.001) and total (65.4±12.4 vs 54.6±16.4, p<0.001). COPD patients with sarcopenia had a significantly greater BODE index (5.7±2.6 vs 3.5±2.3, p<0.001) and higher CCI score (3.3±1.3 vs 2.3±1.3, p<0.001) than those without sarcopenia. Body composition analysis showed that compared to the group without sarcopenia, male patients with sarcopenia had a significantly higher BMI (23.2±5.7 vs 28.1±6.4, p<0.001), FMI (5.6±4.3 vs 8.1±6.4, p=0.014), SMI (6.7±1.4 vs 9.0±1.2, p<0.001), and visceral fat (8.4±6.5 vs 12.1±7.1, p=0.002). In addition, after assessing muscle strength and physical performance, male patients with sarcopenia showed significantly lower hand-grip strength (21.3±5.3 vs 37.2±10.8 kg, p<0.001), gait speed (0.61±0.32 vs 0.96±0.29 m/s, p<0.001) and shorter 6MWT distance (221.3±116.3 vs 345.2±103.6 m, p<0.001). Patients with sarcopenia also had a significantly higher Borg score (post 6MWT) than persons without (6.7±3.3 vs 4.1±2.4, p=0.021). Female patients with sarcopenia significantly differed from those without sarcopenia only in SMI (5.2±0.3 vs 7.1±0.9 kg/m², p=0.009).

Factors from Table 1 such as age, acute exacerbation of COPD, CAT, FEV₁, BODE index, CCI, Borg score (post 6MWT), SGRQ symptoms, SGRQ activity, SGRQ impact, BMI, fat mass index, visceral fat, gait speed, and 6MWT distance, were included in a binomial logistic regression model as possible predictors of sarcopenia. The binomial logistic regression analysis showed that risk of sarcopenia increases with higher level of visceral fat (OR=1.968; 95% CI: 1.250–3.100, p=0.003), age (OR=1.228; 95% CI: 1.042–1.448, p=0.001), SGRQ activity score (OR=1.205; 95% CI: 1.024–1.417, p=0.024) and lower BMI (OR=0.278; 95% CI: 0.126–0.614, p=0.002) (Table 2).

### Table 2. Factors associated with sarcopenia

|                      | OR    | 95% CI            | p*     |
|----------------------|-------|-------------------|--------|
| Age                  | 1.228 | 1.042–1.448       | 0.015  |
| BMI                  | 0.278 | 0.126–0.614       | 0.002  |
| Visceral fat         | 1.968 | 1.250–3.100       | 0.003  |
| SGRQ Activity        | 1.205 | 1.024–1.417       | 0.024  |

*p<0.05 is statistically significant.
DISCUSSION

We assessed the prevalence of sarcopenia among a group of COPD patients in Ukraine and Poland. We found that sarcopenia was present in 25.3% of COPD patients, and 6.3% of recruited COPD patients suffered from severe sarcopenia. Our results showed a slightly higher prevalence of sarcopenia compared to 21.6% given in a recent meta-analysis by Benz et al. There are several possible explanations for the slightly higher percentage of sarcopenia patients in our study: different disease severity and gender proportions of the study population and low adoption of pulmonary rehabilitation programs among COPD patients in our countries.

We found that sarcopenia affected 46 male patients (26.7%) and 2 female patients (11.1%). Compared with those without sarcopenia, the group of COPD patients with sarcopenia was characterized by a significantly higher percentage of men (95.8% vs 88.7%, p < 0.001) and a lower percentage of women (4.2% vs 11.3%, p < 0.001). Severe sarcopenia was absent among females while it affected 12% of male patients (95.8% vs 88.7%, p < 0.001) and a lower percentage of men (95.8% vs 88.7%, p < 0.001). Severe sarcopenia was characterized by a significantly higher BODE index than patients without sarcopenia, however, we found that patients with sarcopenia had a significantly higher BODE index than patients without sarcopenia (5.7±2.6 vs 3.5±2.3, p<0.001) (Table 1).

The level of visceral fat being the strongest factor associated with sarcopenia also could be explained by specific changes in the body caused by ageing. Couillard et al. described this mechanism by alteration of steroid hormone profile in elderly men which results in fat redistribution from subcutaneous to visceral deposition. Furthermore, Furutate et al. showed that COPD patients with advanced stages of disease presented with excessive visceral fat despite the absence of obesity. According to their view, it was developed due to decrease physical inactivity among patients with severe COPD, leading to excess visceral fat accumulation.

According to our results, reduced daily physical activity based on SGRQ was another factor strongly associated with the development of sarcopenia among COPD patients (OR=1.968, p=0.003). Discovering this association is extremely important because it explains the main mechanism of its appearance among persons with COPD. Low physical activity appears due to subjective feeling that restricts performing movement and leads to the appearance of sarcopenia. Such limitation is mainly based on airflow limitation, but it better reflects in the appearance of sarcopenia than FEV₁ because different persons perceive in different ways the same level of airflow obstruction. Joppa et al. reported higher SGRQ physical activity of COPD patients with sarcopenic obesity than patients with normal body composition. Jones et al. already presented the same effect on skeletal muscle using specific questionnaires and accelerometer to evaluate physical activity. This finding improves our understanding of sarcopenia among COPD patients and requires further research.

We found a significant negative association between sarcopenia and BMI (OR=0.278, p=0.002). Similar associations between sarcopenia and gender, smoking status including current and ex-smokers, BMI among nursing home residents in Turkey were found by Tasar et al. Similar associations between sarcopenia and gender, smoking status including current and ex-smokers, BMI among nursing home residents in Turkey were found by Tasar et al. Similar associations between sarcopenia and gender, smoking status including current and ex-smokers, BMI among nursing home residents in Turkey were found by Tasar et al. Similar associations between sarcopenia and gender, smoking status including current and ex-smokers, BMI among nursing home residents in Turkey were found by Tasar et al. Similar associations between sarcopenia and gender, smoking status including current and ex-smokers, BMI among nursing home residents in Turkey were found by Tasar et al.
suffered from more comorbidities and had higher Charlson comorbidity index compared to the control group (3.3±1.3 vs 2.3±1.3, p<0.001) (Table 1). We did not find associations with different categories of comorbidities as separate predictors, in contrast to our previous research where we revealed significant worse skeletal muscle impairment among COPD patients than coronary artery disease, despite several common predictive factors for sarcopenia. Other authors presented data showing significant associations between comorbidities and sarcopenia. Tda et al. showed that COPD female patients with sarcopenia were significantly more likely to be affected with diabetes mellitus than male patients with osteoarthritis. Sousa et al. in their research proved the role of sarcopenia as an independent factor related to increasing hospitalization costs. They also found that sarcopenia usually affected males with greater Charlson comorbidity index score.

Patients with sarcopenia had significantly worse FEV₁ than patients without sarcopenia (40.0±17.0 vs 47.7±17.3, p=0.008) (Table 1), however such airflow limitation was not a predictive factor for sarcopenia among COPD patients that confirmed the results of Costa et al. Nevertheless, in most studies, sarcopenia was associated with these factors. Vestbo et al. demonstrated that skeletal muscle quantity decreased with increasing severity of COPD. Thus, in GOLD stage 1 low FFMI was present in a quarter of the patients and GOLD stage 4 approximately 50% of COPD patients had low FFMI.

Limitations

Our study has some limitations. We used bioelectrical impedance analysis instead of ‘gold standards’ for non-invasive evaluation of skeletal muscle quantity such as magnetic resonance imaging (MRI) or computed tomography (CT). We choose this equipment because it was affordable and portable, taking into account settings in which our research has been performed. We used SGRQ to assess physical activity limitation instead of specific questionnaires such as the modified Minnesota Leisure-time Physical Activity Questionnaire, multisensory accelerometer and multiple physiological measures to calculate energy expenditure. Other limitations were the small study population, cross-sectional design, absence of assessments of pre-existing malnutrition of patients, the unbalanced composition of the population based on the GOLD groups and gender with the predominance of group B and C and male patients.

CONCLUSIONS

Sarcopenia affected almost every fourth COPD patient; it was present in 25.3% of all patients with COPD. Only male COPD patients suffered from severe sarcopenia with a prevalence of 6.3%. Sarcopenia was associated with older age, low body mass index, high level of visceral fat and limited physical activity.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

This work was supported by the ‘PROM Programme – International scholarship exchange of PhD students and academics for implementing a short form of education’ (project No. POWR.03.03.00-IP08-00-P13/18) and by a Silesian Medical University grant (KNW-1-103/N/9/K).

ETHICAL APPROVAL AND INFORMED CONSENT

The study was approved by the local ethics committees at the National Pirogov Memorial Medical University, Vinnytsya, Ukraine (No. 9 01.11.2018) and Medical University of Silesia, Katowice, Poland (PCM/0022/KB1/53/19). All participants filled in an informed consent form for the study.

DATA AVAILABILITY AND SHARING

The data supporting this research is available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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