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Systematic review

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Prevalence of sarcopenia in Chronic Obstructive Pulmonary Disease: systematic review

Prevalência de sarcopenia na Doença Pulmonar Obstrutiva Crônica: revisão sistemática

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RESUMO | INTRODUÇÃO: A DPOC está associada a um processo inflamatório sistêmico que pode causar sarcopenia, redução da função e massa muscular, embora sua frequência e intensidade não seja completamente conhecida em portadores dessa enfermidade. **OBJETIVO:** descrever a prevalência e métodos de identificação da sarcopenia na DPOC através de uma revisão sistemática. **MATERIAIS E MÉTODOS:** Revisão sistemática utilizando a metodologia PICo e palavras-chave (*Chronic Obstructive*, *Pulmonary Disease, Sarcopenia*). Foram incluídos estudos publicados que estimaram a prevalência de sarcopenia na DPOC. Excluídos aqueles cujo método não detalhou o diagnóstico da sarcopenia. **RESULTADOS:** A pesquisa resultou inicialmente em 897 artigos. Desses, 877 foram excluídos, sendo 20 selecionados (15 transversais, cinco longitudinais, um caso/controle). As amostras variaram de 57 a 2.582 participantes, a maioria (70%) conduzida em ambulatório. Um estudo foi de base populacional. A idade média foi de 66 anos. A prevalência de sarcopenia na DPOC variou de 4,4% a 86,5%. Os métodos diagnósticos utilizados para determinar massa muscular foram a Absortometria Radiológica de Dupla Energia (DEXA), a bioimpedância, a bioimpedância e as equações de referência. A força muscular foi estimada utilizando-se a preensão manual em dinamômetros portáteis ou a flexão/extensão do joelho através do dinamômetro isocinético. A capacidade funcional foi avaliada pelo teste de caminhada dos seis minutos ou teste de velocidade da marcha. **CONCLUSÃO:** A prevalência de sarcopenia na DPOC encontrada nos estudos (4,4 a 86,5%) é muito variável; e é influenciada não somente pela característica do paciente, mas também pelo local, delineamento e método diagnóstico utilizado. Uma padronização de métodos parece ser necessária para se uniformizar condutas na literatura.

PALAVRAS-CHAVE: Doença pulmonar obstrutiva crônica. Prevalência. Sarcopenia. Métodos diagnósticos.

ABSTRACT | INTRODUCTION: COPD is associated with a systemic inflammatory process that can cause sarcopenia, reduced function and muscle mass, although its frequency and intensity is not completely known in patients with this disease. **OBJECTIVE:** To describe the prevalence and methods of identifying sarcopenia in COPD through a systematic review. **MATERIALS AND METHODS:** Systematic review using the PICo methodology and keywords (Chronic Obstructive, Pulmonary Disease, Sarcopenia). We included published studies that estimated the prevalence of sarcopenia in COPD. Excluding those whose method did not detail the diagnosis of sarcopenia. **RESULTS:** The search resulted initially in 897 articles. Of these, 877 were excluded, of which 20 were selected (15 transverse, five longitudinal, one case / control). Samples ranged from 57 to 2,582 subjects, the majority (70%) conducted on an outpatient basis. One study was population-based. The mean age was 66 years. The prevalence of sarcopenia in COPD varied ranged from 4.4% to 86.5%. The diagnostic methods used to determine muscle mass were Dual X-ray Absorptiometry (DEXA), bioimpedance and reference equations. Muscle strength was estimated using manual gripping on portable dynamometers or knee flexion / extension through the isokinetic dynamometer. Functional capacity was assessed by the six-minute walk test or gait speed test. **CONCLUSION:** The prevalence of sarcopenia in COPD (4.4 to 86.5%) is very variable; and is influenced not only by the patient´s characteristic, but also by the location, study design and diagnostic method used. A standardization of methods seems to be necessary to standardize conducts in the literature.

KEYWORDS: Chronic obstructive pulmonary disease. Prevalence. Sarcopenia. Diagnostic methods.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important global health problem that mainly affects the elderly. It is characterized by persistent obstruction of the airways and presence of emphysema and/or chronic bronchitis[1]. The inflammatory manifestation of the disease has a systemic profile[2] and directly affects the musculoskeletal system, causing muscular atrophy[3] of peripheral limbs, osteoporosis, change in fiber type[4,5] (an independent predictor of mortality in subjects with severe to very severe COPD[6], decreased protein synthesis, muscle depletion[7], loss of strength and decline in functional capacity[8], resulting in several comorbidities such as sarcopenia.

Sarcopenia is a disorder characterized by reduced strength and muscle mass, which may be accompanied by poor physical performance, being the strength currently the most reliable criterion of evaluation of muscular function[9-12]. This condition is associated with an increased risk of falls, fractures[10,13], physical disability[9], reduction of quality of life[14], cognitive impairment[15], presence of heart disease[16] and respiratory[17], and mortality[9].

This syndrome has been associated with aging, but it is recognized that the development of sarcopenia begins earlier[18], being usually multifactorial, involving mitochondrial dysfunction, hormonal changes, decline in neural function, caloric-protein malnutrition, reduction of satellite cells, chronic inflammation, worsening of lifestyle[10] and weight loss[11]. The consequences of these metabolic pathways are a decrease in resting energy expenditure, of insulin sensitivity and muscle strength[10].

Cellular pathways that relate chronic inflammation to sarcopenia are well sedimented[10,12,13]. In general, the activation of the proteolytic pathway ubiquitin proteasome seems to be involved, causing muscle protein imbalance; decreased mitochondrial transcription factors (Fox, NF-κB, NRF1); apoptosis caused by apoptotic cascade activating proteins; inhibition of factors that regulate cell survival activity (MAPKS, Bcl-2, Akt, Caspases); and suppression of the cascade signaling cycle and cell survival, migration and protein synthesis (PI3K/Akt/mTOR), activated by the hormone IGF-1 and insulin.

Sarcopenia, as well as functional alterations, are significant clinical findings in subjects with COPD[14]. Individuals with this concomitant dysfunction have more severe dyspnea symptoms, less exercise tolerance, more frequent exacerbations and worse prognosis[2]. When the subjects present in addition to the reduction in strength and muscle mass, poor physical performance, sarcopenia is considered severe[9]. As a result, various tools and methods for diagnosis and evaluation still be developed and updated.

Thus, recognizing the prevalence and diagnostic methods of sarcopenia is a very important effort in the search for effective strategies of prevention and intervention that can treat this syndrome and maintain the physical functionality of individuals. Therefore, is necessary in order review studies that evaluate, besides pulmonary function, the body composition, muscle strength and physical performance of these subjects. This fact corroborates the growing interest in muscle function and the search for progress in understanding the pathophysiology and therapeutic potential of systemic COPD[15,16]. Thus, the aim of this article is to systematize the knowledge about the prevalence of sarcopenia in people with COPD and to evaluate the appropriate diagnostic methods of this syndrome.

Materials and methods

This is a systematic review and the guiding question of this study was: "What is the prevalence of sarcopenia in COPD patients and what are the diagnostic methods used?" The research was structured from the PICo strategy[26], an acronym for Population (individuals with COPD), Interest (sarcopenia and diagnostic methods) and Context (prognosis, disease severity, muscle dysfunction, quality of life, mobility, exacerbations). The following databases were systematically searched: PubMed, SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Health Sciences Literature) e Science Direct. Key words were used: Pulmonary Disease, Chronic Obstructive; Sarcopenia; synonyms and related words plus boolean operators "AND" and "OR", according to the Descriptors in Health Sciences (DeCS), as showed in Chart 1. The search

was carried out from March to May 2018. Screening was performed using the words found in the titles, subjects, and summaries of articles.

Chart 1. Keywords used in the electronic search plus the boolean operators "AND" and "OR"

Keyword	Synonyms and Related Keywords
Pulmonary Disease, Chronic Obstructive	Airflow Obstructions, Chronic; Chronic Airflow Obstructions; Airflow Obstruction, Chronic; Chronic Airflow Obstruction; Chronic Obstructive Airway Disease; Chronic Obstructive Lung Disease; Chronic Obstructive Pulmonary Disease; COAD; COPD.
Sarcopenia	Sarcopenias

Source: DeCS - Health Sciences Descriptors, 2018.

It was included published studies that estimated the prevalence of sarcopenia in COPD subjects duly diagnosed by spirometry according to the GOLD criteria[27], and may be experimental and/or observational research using primary or secondary data, available in English, Portuguese or Spanish. We excluded studies whose method did not detail the diagnosis of sarcopenia.

The articles collected through the database searches were selected by screening titles (first step), summaries (second stage) and extensive reading (third stage). Then, exploratory reading of the selected studies and, later, selective and analytical reading was performed. Data extracted from the articles: authors, title, journal, year, abstract and conclusions were systematized, in order to obtain information pertinent to the research.

It was used, as an instrument to evaluate the quality of the studies, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[28], composed of 14 criteria: research question, study population, groups recruited from the same population and uniform eligibility criteria, justification of sample size, exposure assessed before outcome measurement, sufficient time to see an effect, different exposure levels of interest, exposure and assessment measures, repeated exposure assessment, measures of results, blindness of evaluators of results, follow-up rate, statistical analyzes. The quality of the articles was classified as good, fair or poor, evaluated by two independent evaluators (NC and AM). If discordances were noted, a third blind evaluator (AA) reviewed the study (or studies).

The selection, extraction of data from the articles and identification of methodological aspects was performed by two independent reviewers. When there was a number disagreement between them, the reviewers read the entire article again for reevaluation. If the divergence persisted, a third impartial reviewer would evaluate and make the final decision.

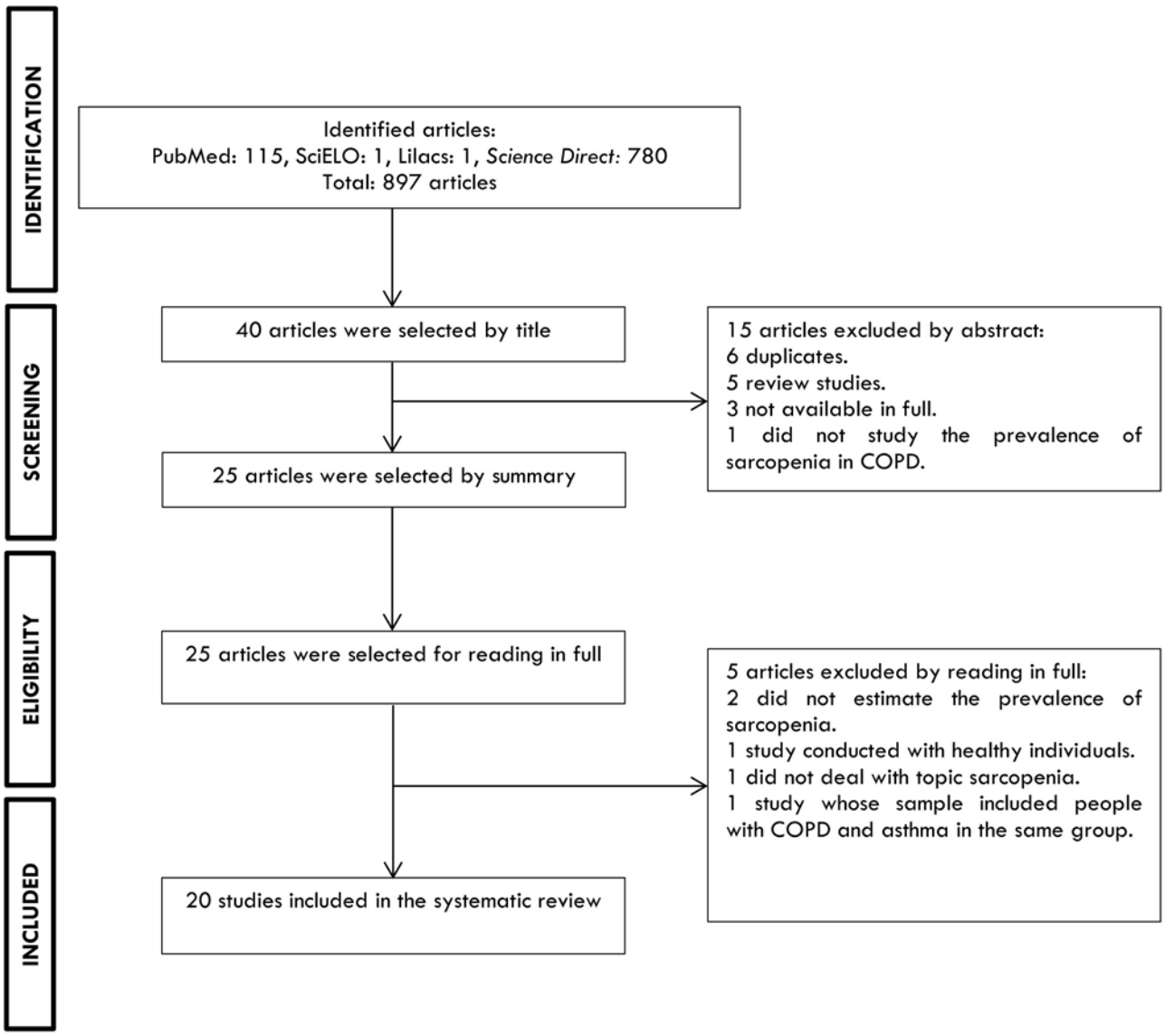
The research followed the checklist PRISMA for systematic reviews[29]. The protocol of the stages of construction of this systematic review was published in the International Prospective Register of Systematic Reviews (PROSPERO), under registration no. CRD42017080966.

Results

The survey initially gave rise to 897 articles. Of these, 855 were excluded, being selected 40 articles on screening of titles. Of the 40 articles, 25 were selected by reading the abstracts that appeared to be meet the selection criteria. However, after reading the articles in full, five of them did not meet all the inclusion criteria, resulting in the ultimate selection of 20 articles (15 of cross-sectional design, five longitudinal and one case/control), according to Figure 1.

The 20 papers were read in an analytical and selective manner and organized in a table with relevant information of the research, as author and year of publication; sample; diagnostic method of sarcopenia; and prevalence of the syndrome in COPD, as shown in Table 1.

Figure 1. Search Flow Diagram



COPD: Chronic Obstructive Pulmonary Disease; DEXA: Dual X-ray Absorptiometry; BIA: bioimpedance analysis; ALM/BMI: Appendicular lean mass/ Body mass index; FFM/h²: fat-free mass/height2; ASM/h²: skeletal muscle mass/height 2; M: male; F: female; RV: reference value; PR: prevalence ratio; PP: Physical performance

Table 1. Study data, diagnostic criteria and prevalence of sarcopenia according to gender, estimated by the authors (n=20), 2018 (to be continued)

Author/ year (country)	Study Design	Sample data	Diagnostic Criteria			Prevalence (%)	PR*
			Muscle mass	Muscle strength	PP		
Costa TMR, 2018[30] (Brazil)	Cross-sectional study	- n=265 - Individuals with COPD: n=121 (F=65, M=56, mean age: 67.9 ± 8.6 years) - Smokers without COPD: n=63 (F=29, M=34, mean age: 65.5 ± 8.9 years) - Never smoked and without COPD: n=81 (F=47, M=34, mean age: 66 ± 8.5 years). - GOLD: A=29, B=29, C=34 e D=29.	- Method : DEXA - Index: ALM/BMI - Cut-off (kg/m²): M=0.789 F= 0.512	-	- Method: Gait speed - Cut-off (m/s): <0.8	-Total: 12.4	3.5
Trajanoska K, 2018[31] (Netherlands)	Cohort	- n=5911 - COPD: n=882 (mean age: 69.2 years). - Without COPD: n=5029.	- Method : DEXA - Index: ALM/h² - Cut-off (kg/m²): M=≤7.25 F=≤5.67	- Method: Hydraulic Hand dynamometer -Cut-off (kg/m²): M≤29 (if BMI ≤24), M≤30 (if BMI ≤24.1-28), M≤32 (if BMI >28). F≤17 (if BMI ≤23), F≤17.3(if BMI ≤23.1-26), F≤18 (if BMI >26.1-28), F≤21 (if BMI >29).	- Method: Gait speed - Cut-off(m/s): M<0.65 (if h≤173 cm), M<0.76 (if h>173 cm). F<0.65 (if h≤159 cm), F<0.76 (if h>159 cm).	-Total: 4.4 -M: 1.65 -F: 2.74	3.9-5.0
de Blasio F, 2018[32] (Italy)	Cross-sectional study	- n=263 with stable COPD (M=185, F=78, mean age: 69.8 ± 8.0 years).	- Method : BIA - Index : FFM/h² - Cut-off (kg/m²): M=≤8.50 F=≤5.75	- Method: Hydraulic Hand dynamometer - Cut-off (kg/m²): M<17 F<15	- Method: Gait speed 4m. - Cut-off (m/s): ≤0.8	-Total: 24.0	-
Lee DW, 2017[33] (South Korea)	Cross-sectional study	- n=947 - Asthma: n=89 - COPD: n=748 (M=416, F=331 mean age: 66.23 ± 7.98 e FEV_1 de 78.26 ± 15.35). - Asthma and COPD: n=110.	- Method : DEXA - Index : ASM/h² - Cut-off (kg/m²): M=≤7.0 F=≤5.4	-	-	-Total: 33.5 -M: 14.4 -F: 19.1	-

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Table 1. Study data, diagnostic criteria and prevalence of sarcopenia according to gender, estimated by the authors (n=20), 2018 (continuation)

Author/ year (country)	Study Design	Sample data	Diagnostic Criteria			Prevalence (%)	PR *
			Muscle mass	Muscle strength	PP		
Kneppers AEM, 2017[34] (Netherlands)	Cohort	- n = 105 - COPD: n=92: (M=64, F=28, mean age 65.2 ± 7.9 years). - Healthy individuals: n=13 (M=7, F=6, mean age 64.5 ± 5.4 years). - GOLD: A=3, B=22, C=46 e D=21.	- Method: DEXA - Index: ASM/h² - Cut-off (kg/m²): M=≤7.23 F=≤5.76	-	-	-Total: 41 -M: 31 -F: 10	13
Byun MK, 2017[35] (South Korea)	Cross-sectional study	- COPD: n=80 (M=67, F=13, mean age 68.4 ± 8.9 years). - GOLD: A=24, B=31, C=5, D=20.	- Method: BIA - Index: SSM/h² - Cut-off (kg/m²): M=6.95 F=4.94	- Method: Hydraulic Hand dynamometer - Cut-off (kg/m²): M=≤30 F=≤20	-	-Total: 24.7 -M: 21 -F: 3.7	45
Hwang JA, 2017[36] (South Korea)	Cross-sectional study	- n=777 men with COPD (mean age 63 ± 10.6 years). - GOLD: A=335, B=390, C e D=52.	- Method: DEXA - Index: ASM/h² - Cut-off (kg/m²): M=6.95 F=4.94	-	-	-Total: 8.3 -M: 8.3	1.27
Lee DW, 2016[37] (South Korea)	Cross-sectional study	- n=858 (M=641, F=217, mean age 66.27 ± 7.88 years).	- Method: DEXA - Index: ASM/h² - Cut-off kg/m²): M=≤7.0 F=≤5.4	-	-	-Total: 33.3 -M: 26.1 -F: 7.2	-
Pothirat C, 2016[38] (Thailand)	Cross-sectional study	- n=121 subjects with stable COPD	- Method: BIA - Index: : FFM/h² - Cut-off (kg/m²):M=≤16 F =≤15	-	-	-Total: 9.9	8.3
Lipovec NC, 2016[39] (Slovenia)	Prospective observation	- n=112 with COPD (M=74, F=38, mean age 66 ± 8 years). -GOLD: B=17%, C=52%, D=31%.	- Method: DEXA - Index: ASM/h² - Cut-off (kg/m²): M=≤7.23 F=≤5.67	-	- Method: Six Minute Walk Test - Cut-off (m/s): <0.8	-Total: 54.1 -M: 39.1 -F: 15	17

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Table 1. Study data, diagnostic criteria and prevalence of sarcopenia according to gender, estimated by the authors (n=20), 2018 (continuation)

Author/ year (country)	Study Design	Sample data	Diagnostic Criteria			Prevalence (%)	PR*
			Muscle mass	Muscle strength	PP		
Joppa P, 2016[40] (Slovakia)	Observational longitudinal and prospective	- n=2582 - COPD: n=2000 (M=1314, F=686, age 40 - 75 years). - Without COPD: n=582 (337 smokers and 245 non-smokers, M=272, F=276, age 40 – 75 years).	- Method: BIA - Index: FFM/h² - Cut-off (kg/m²): ≥90%	-	- Method: Six Minute Walk Test - Cut-off (m/s): <0.8	-Total: 24.2 -M: 17 -F: 7.2	1.5
van de Bool C, 2016[41] (Netherland)	Cross-sectional study	- n= 97 - COPD: n=45 (M=28, F=17, age between 59 and 67 years). - Without COPD: n=52 (M=32, F=17, age between 59 and 67 years).	- Method: DEXA - Index: FFM/h² - Cut-off (kg/m²): M=≤7.23 F=≤5.67	-	-	-Total: 31 -M: 28.8 -F: 2.2	-
Costa TM, 2015[42] (Brazil)	Cross-sectional study	- n=91 with COPD (M=41, F=50, mean age 67.4 ± 8.7 years). - GOLD: A=15, B=22, C=34, D=20.	- Method: DEXA - Index: ALM/h² - Cut-off (kg/m²): M=≤7.26 F=≤5.45	-	-	-Total: 39.4 -M: 21.9 -F: 17.5	1.19
Ramos D, 2015[43] (Brazil)	Cross-sectional study	- n=57 with COPD (M=37, F=20).	- Method: DEXA - Index: ALM/h² - Cut-off (kg/m²) M=≤7.914 F=≤5.52	- Method: Dynamometer (knee flexion/extension) - Cut-off (kg/m²): Flexion: M=112; F=72.7. Extension: M=206; F=144.5	- Method: Six Minute Walk Test - Cut-off (m/s): <0.8	-Total: 43.8 -M: 33.3 -F: 10.5	-
van de Bool C, 2015[44] (Netherland)	Cross-sectional study	- n=505 with COPD (M=287, F=218 mean age 64 years). -GOLD: A=7,9%, B=40,8%, C=39,8%, D= 11,5%.	- Method: DEXA - Index: ASM/h² - Cut-offs (kg/m²): M=≤7.23 F=≤5.67	- Method: Isokinetic dynamometer (knee flexion/extension). - Cut-off (kg/m²): Uninformed	- Method: Six Minute Walk Test and cycle ergometer - Cut-off (m/s): Best value of two walk tests	-Total: 86.5 -M: 47 -F: 39	-
Jones SE, 2015[45] (England)	Case-control	- n=622 with COPD (M=254, F=268, mean age 66 years).	- Method: BIA - Index: SMM/h² - Cut-off (kg/m²): M=≤8.5 F=≤5.75	- Method: Portable hydraulic dynamometer - Cut-off (kg/m²): M=≤30 F=≤20	- Method: 4 – metre gait speed - Cut-off (m/s): ≤0.8	-Total: 28.4 -M: 16.1 -F: 12.3	-

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Table 1. Study data, diagnostic criteria and prevalence of sarcopenia according to gender, estimated by the authors (n=20), 2018 (conclusion)

Author/ year (country)	Study Design	Sample data	Diagnostic Criteria			Prevalence (%)	PR*
			Muscle mass	Muscle strength	PP		
Chung JH, 2015[46] (South Korea)	Cross-sectional study	- n=8.145 -COPD: n=1039 (M=760, F=279, mean age 64.5 ± 9.4 e 64.5±10.2 years, respectively). - Restrictive phenotype: n=1029 (M=511, F=518, mean age 60.0 ± 11.1 e 61.3 ± 1.8 years) -Control: n=6077 (M=2346, F=3731, mean age 53.2 ± 9.7 e 55.4 ± 10.4 years). - GOLD: A=473, B=500, C=58, D=8.	- Method: BIA - Index: ASM/h² -Cut-off (kg/m²): M=≤6.95 F=≤4.95	-	-	-Total: 44.7 -M: 32.7 -F: 12	1.17
Gologanu D, 2014[47] (Romania).	Cross-sectional study	- n=36 with COPD (M=33, F=3, mean age 65.6 ± 7.5 years). - GOLD: B=14, C=15, D=7.	- Method: DEXA - Index: FFM/h² - Cut-off (kg/m²): M=≤16 F=≤15	-	-	-Total: 8.3	-
Koo HK, 2014[48] (South Korea)	Cross-sectional study	- n=574 men (mean age 62.6 ± 0.7 years). - GOLD: A=46,3%, B=48,6%, C e D=5,1%.	- Method: DEXA - Index: ASM/peso x 100 - Cut-off (kg/m²): 29.8%	-	-	-Total: 29.3	-
Sergi G, 2006[49] (Italy).	Cross-sectional study	- n=86 - COPD: n=40 (mean age 75.7± 5.3 years). - Without COPD: n=46 (mean age 77.7 ± 7.0 years).	- Method: DEXA - Index: ASM/h² - Cut-off (kg/m²): M=≤7.26	-	-	-Total: 38	1.2

COPD: Chronic Obstructive Pulmonary Disease; DEXA: Dual X-ray Absorptiometry; BIA: bioimpedance analysis; ALM/BMI: Appendicular lean mass/ Body mass index; FFM/h²: fat-free mass/height2; ASM/h²: skeletal muscle mass/height 2; M: male; F: female; RV: reference value; PR: prevalence ratio; PP: Physical performance

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In relation to the general characteristics of the articles (Table 1), predominantly cross-sectional studies (75%), with publications from 2006 to 2018. Most studies were conducted in Europe (four in the Netherlands, two in Italy, one in Slovenia, one in Slovakia, one in Romania and one in England); in Asia (six in South Korea, one in Thailand); and in South America (three in Brazil).

The mean age of the subjects was 66 years. The prevalence of sarcopenia in COPD subjects assessed by the various diagnostic methods in the reviewed (n = 20) varied from 4.4% to 86.5%. When related to gender, the prevalence ranged from 1.65% to 47.5% for men and 2.2% to 19.1% for women. In relation to the GOLD stage, the variation was from zero to 22.7% for GOLD A; 8.3% to 45% for GOLD B; 6.7% to 71% for GOLD C and 14.3% to 58.3 for GOLD D. The prevalence estimated by European studies (n = 10) ranged from 4.4% to 86.5%; in South American (n = 3) from 12.4% to 44.8%; and from 8.3% to 33.5% in Asians (n = 7).

Muscle mass assessment was made in all studies (Table 1). The most widely used diagnostic methods for mass measurement were DEXA and BIA. DEXA was applied to 70% of the studies and the BIA was used in 30%. Muscle strength was evaluated in six articles, in which 66% used manual gripping with portable dynamometers and 33% used knee flexion / extension through an isokinetic dynamometer. Functional capacity was calculated in only seven studies. Among them, 57% used the six-minute walk test and 42% used walking speed.

Ten studies (50%) exclusively used muscle mass as a diagnostic criterion for sarcopenia: one (5%) considered mass and strength; four (20%) included mass and functional capacity, and five (25%) included mass, strength and performance, as recommended by the European Sarcopenia Consensus[19].

Among the studies that used DEXA as a diagnostic method, 12 (60%) used the appendicular muscle mass index (IMMA), defined as the sum of the arm and leg fat free mass (in kg) divided by the square of the height (in meters) and two (10%) used the fat free muscle mass index (calculated by dividing the appendicular mass and the mineral content bone by height square in meters). Of the articles that used the BIA as a diagnostic method, three (15%) used the IMMA and three (15%) fat free muscle mass index.

All articles presented the research question or objective clearly. The population was not precisely specified in five studies[40,43,47-49] and the participation rate of eligible individuals in the twenty articles was at least 50%, justifying the size of the samples. However, in three surveys, participants were not enabled or recruited in the same time frame.

Only four studies[34,38,43,46] showed justification of the sample size. In 16 articles the evaluations were not presented before the measurement of the results, there was not enough time to observe the effect and also the individuals were not evaluated more than once over time due to the type of study design used, the cut transverse.

All articles examined different levels of exposure and the measures were clearly defined, valid and reliable, including tools or methods to measure outcomes. In none of the twenty studies did blinds the evaluators of the results, nor were their high rates of follow-up loss in the studies. The main variables were measured and statistically adjusted for their impact on the interface between exposure and outcome in all studies.

Table 2. Quality evaluation of the reviewed articles (n = 20)

Research	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality
Costa TMR, 2018[30]	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y	N	Y	Y	Good
Trajanoska K, 2018[31]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Fair
De Blasio F, 2018[32]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	Y	Y	Good
Lee DW, 2017[33]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	Y	Y	Good
Kneppers AEM, 2017[34]	Y	Y	Y	N	N	Y	N	NA	Y	N	Y	N	Y	Y	Good
Byun MK, 2017[35]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	Y	Y	Good
Hwang JA, 2017[36]	Y	Y	Y	Y	N	NA	NA	NA	Y	N	Y	N	Y	Y	Good
Lee DW, 2016[37]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	Y	Y	Good
Pothirat C, 2016[38]	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	Y	Y	Good
Lipovec NC, 2016[39]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Good
Joppa P, 2016[40]	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	N	Y	Y	Fair
Van de Bool C, 2016[41]	Y	Y	Y	Y	NA	NA	N	NA	Y	NA	Y	N	Y	Y	Good
Costa TM, 2015[42]	Y	Y	Y	Y	NA	NA	N	Y	Y	N	Y	N	Y	Y	Good
Ramos D, 2015[43]	Y	N	Y	Y	N	NA	N	N	Y	N	Y	N	Y	Y	Good
Van de Bool C, 2015[44]	Y	Y	Y	Y	NA	NA	N	Y	Y	N	Y	N	Y	Y	Good
Jones SE, 2015[45]	Y	Y	Y	Y	NA	NA	N	Y	Y	N	Y	N	Y	Y	Good
Chung JH, 2015[46]	Y	Y	Y	Y	N	NA	N	Y	Y	N	Y	N	Y	Y	Good
Gologanu D, 2014[47]	Y	N	Y	Y	NA	NA	N	Y	Y	N	Y	N	Y	Y	Fair
Koo HK, 2014[48]	Y	N	Y	Y	NA	NA	N	Y	Y	N	Y	N	Y	Y	Fair
Sergi G, 2006[49]	Y	N	Y	Y	NA	NA	N	N	Y	N	Y	N	Y	Y	Fair

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Y, yes; N, no; CD, cannot determine; NA, not applicable; NR, not reported.

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Discussion

The present systematic review of the literature provides a broad spectrum of the prevalence of sarcopenia in people with Chronic Obstructive Pulmonary Disease. To our knowledge, this is the first systematic review to evaluate this specific evidence in COPD. It was shown a large variation in prevalence (4,4%-86,5%), thought to be due to: variability in the various diagnostic tools presented in the literature;different reference values; different cutoff points; broad age ranges and geographical variations[50].

COPD can be considered a relevant risk factor for sarcopenia[50]; the prevalence of sarcopenia was higher in people with COPD than in those without COPD[51] (7.5% - 77.6%). This syndrome seems to occur in response to increased catabolism, elevated proinflammatory cytokines, and increased oxidative stress[30]. The highest frequencies of sarcopenia occurred in GOLD C and D COPD stages[32,34,39,41,45], revealing the relationship between sarcopenia and frequent exacerbations, more intense symptoms and greater severity of the disease[30,35,45].

Sarcopenia was also linked to a worse airflow limitation, especially in patients with COPD. This data was defined in large part of the studies that made the analysis between the sexes[34-35,37,39-46]. In males, both sarcopenia classifications appear to be associated with smoking, reduction in lower limb function, as well as a lower level of physical activity and impaired health. Among women, there is a greater association with height, fat mass and alteration in lower limb function. Also, between men and women there is a difference in the trajectory of skeletal muscle decline with aging. In men, there is a gradual decline, whereas in women there is a tendency to get a sudden fall in muscle mass and function after menopause[52]. Hereditary deficiency of alpha-1 antitrypsin, airway hyperresponsiveness, low birth weight, severe respiratory infections in childhood, and low socioeconomic status is related to a prevalence of COPD in adulthood, usually in individuals with age over 40 years[53]. The mean age of subjects with COPD who participated in the study was 66 years.

The main parameters involved in the diagnosis of sarcopenia are muscle strength, quantity and quality of muscle mass and its function, measurable through measures of skeletal muscle mass, strength and physical performance of the subjects[9]. There was little agreement between the diagnostic criteria for sarcopenia. The results of the present study shows that the diagnostic criteria of sarcopenia were very divergent and diverse, and this aspect represents an important limitation because they influence the estimation of sarcopenia prevalence[54], as well as relevant discrepancies in the measurements of strength and functional capacity in the studies, as criteria for the diagnosis. Some studies in this review presented limitations due to the evaluation methods variation and different cutoff points used for muscle mass and strenght, physical performance and some inconsistent approaches or lack of discussion when reporting results for different age groups. Maybe a standartization of methods should be required in the literature in order to permit comparison between differents results published around the world.

Regarding muscle mass assessment, DEXA was the method most used in the studies. DEXA is an accurate method to estimate the amount of fat, bone mass and lean mass in the body, and does not offer significant risks to subjects due to its minimal radiological exposure, being able to restrict itself only to an area of the body[55]. The cutoff points for DEXA are derived from values of a young adult reference population, specifically two standard deviations below the mean appendicular lean mass for each sex divided by the squared height[31,33,34,36,37,39,42-44,49]. Therefore, the application of these cutoff points exhibits a high variation even when performed in the same continent, in people of similar age group or of the same nationality, thus providing heterogeneous prevalence.

The principle of BIA is that biological tissues act as conductors and the flow of electric current will follow the path of least resistance in the body. Thereby, the apparatus projects a low frequency electric current through the body of the subject and the resistance to that flow is measured by the impedance evaluator56. The BIA was used in fewer studies (30%), however, it is a method that presents a good correlation between the measured muscle mass in relation to DEXA, with a standard error of 9%, probably due

to the influence of body water in determining muscle mass[57].

Dynamometry was used in all studies that evaluated muscle strength. It is a simple, accessible measure and can be widely used in clinical practice to also predict the loss of muscle mass, which allows the application of more appropriate therapies[43].

Among the limitations of the studies, the difficulty in using high accuracy instruments in the diagnosis of sarcopenia is highlighted, since, for the most part, they are not the gold standard for mapping body composition[54]. Standard gold scans are used to estimate skeletal muscle mass on computed tomography and magnetic resonance imaging, considered very accurate imaging systems, which separate the fat from other soft tissues of the body; however, are expensive and limited access exams, in addition to generating radiation exposure[58].

Regarding the methodological limitations of the reviewed studies, the disadvantage of some analyzes due to the cross-cutting nature of most articles, difficulty in analyzing different levels of exposure, insufficient time for authors to wait for possible associations between exposure and outcome and inability to analyze exposures more than once over time[28].

Conclusion

Due to the results found, it was shown that sarcopenia prevalence in COPD subjects is frequent- specially in male and in severe COPD disease, and its variability and heterogenicity are due to individual characteristics, geographic influences, different study designs and different diagnostic criteria. Future research is desirable to standardize methods to identify sarcopenia and to guide clinical practice in order to prevent and treat this systemic and progressive muscular disease, which is also frequent in COPD, and implies in the functional limitations of such subjects.

Authors contributions

The authors Camelier FWR, Cordeiro N, Moreira AVO and Camelier AA elaborated the study design and planned the work. Caria KRSC, Camelier FWR, Cordeiro N, Moreira A and Camelier AA interpreted the final results. Camelier FWR, Cordeiro N, Moreira A and Camelier AA drafted the article. Caria KRSC, Camelier FWR, Cordeiro N, Moreira A, Santos BS, Camelier AA reviewed successive versions and approved the final version of the article.

Conflicts of interest

No financial, legal or political conflict involving third parties (government, private companies and foundations, etc.) was declared for no aspect of the submitted work (including but not limited to grants and funding, advisory board, study design, manuscript preparation, statistical analysis, etc.).

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