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HIGHLIGHT

Morbidity and mortality in COPD patients in Brazi

Anthropometric status of individuals with COPD (PLATINO)

Different exercise intensities in COPD (systematic review and meta-analysis)

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The future is now

Frederico Leon Arrabal Fernandes[1,2,3,a], Suzana Erico Tanni[4,b]

World COPD Day will be held on November 20, 2019. This year's theme is "All Together to End COPD".[1] Participating in this initiative, the JBP publishes this month a special issue with seven articles and three editorials on the topic. It is encouraging to see that various national and international centers do and disseminate their research in this area in our journal. This is further proof that we live at a turning point in COPD care.

We are two months away from 2020. This has great significance for the literature on COPD. Since the article "Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study"[2] was published in 1997, we have found in each original article and review article, and even in the Global Initiative for Chronic Obstructive Lung Disease report,[3] that COPD is expected to become the third leading cause of mortality by 2020. The forecasts were optimistic. That mark was reached in 2016.[4] What we see now is an increase in COPD mortality rates because of the aging of the population. However, when adjusted for age, mortality is seen to decrease, which may be due to the reduction in tobacco consumption that has been observed since the late 20th century.

The course of COPD is favorably affected not only by control of risk factors. Over the last 20 years, the reality of treatment has changed. Once an orphan disease, with no specific treatment and whose pharmacotherapy was most often mistakenly derived from that of asthma, COPD can now be managed with a range of new bronchodilators available in different devices, which allows a personalized choice of medication and form of administration.[5]

Personalization depends on identifying the ideal patient for each treatment. Until recently, the choice was based solely on clinical and functional data, such as dyspnea, pulmonary function, and exacerbation rate. Today, blood eosinophil count is emerging as a biomarker, which can predict response to inhaled corticosteroids.[6] It is then possible to prescribe a medication accurately, avoiding prescribing it to those who would only run the risk of side effects, with no benefits.

The pharmacological approach to COPD has improved significantly, allowing critically ill patients to regain their quality of life. We have second-line medications to prevent exacerbations and, increasingly, ways to prevent harmful readmissions, whether with medications[7] or with home noninvasive ventilation.[8] Although no single drug has been shown to have proven benefits in decreasing mortality, we know that the combination of pharmacological and nonpharmacological care results in reduced exacerbation rates, improved pulmonary function, and increased quality of life.

Providing appropriate treatment that impacts the natural history of the disease has led to a paradigm shift. The treatment that is currently used for more advanced stages of COPD is starting to be prescribed for mild COPD, with a decreased rate of decline in FEV_1 due to the use of bronchodilators at earlier stages of the disease.[9] There is also discussion on the diagnosis of early COPD, that is, on how to diagnose the disease before the onset of obstruction as defined by the spirometry criterion of $FEV_1/FVC < 0.70$. Risk factors, CT-detected emphysema, accelerated lung function decline, and FEV_1/FVC ratio below the lower limit of normal appear to be markers of early disease.[10]

Studies into the various stages of COPD have also advanced the understanding of the natural history of the disease. Temporal parametric analysis of lung density on inspiratory and expiratory CT scans has shown that it all begins with impairment of the small airways, with the possibility of progression to emphysema. In addition, large cohort studies have shown that the presence of symptoms is a predictor of future risk of COPD in those who still do not present with respiratory impairment as determined by spirometry, with this risk being associated with increased exacerbation rates.[11,12] These findings helped to correct, in the Global Initiative for Chronic Obstructive Lung Disease report,[3] the historical error that symptoms were not part of the disease definition.

Within a short time, we began to understand COPD better, diagnose it earlier, and treat it both with drugs and with rehabilitation and other nonpharmacological measures. We use biomarkers to personalize treatment and we can choose the appropriate device for each patient. It looks like the future has arrived. And with it, new challenges. It is necessary to decrease underdiagnosis. It has been estimated that more than 75% of people who have COPD have yet to be diagnosed. We need to broaden knowledge of these new concepts among specialists and nonspecialists and, most importantly, to ensure access to appropriate treatment for all patients.

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The need for a national perspective to improve COPD management

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It is well known that COPD is a leading cause of morbidity and mortality worldwide. Even if the mechanisms can be considered universal, the disease is the result of a complex interplay between exposure (to noxious gases and particles) and host factors (not only genetic factors but also airway hyperresponsiveness and poor lung growth during childhood).[1] Because these conditions may vary considerably between countries and regions, local data are fundamental to obtain a clear picture of the problem and to understand how to deal with the emerging COPD pandemic. Some studies have analyzed data for regions that are considered homogeneous, one such study being the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease) study,[2] which examined the prevalence of COPD in large cities in five Latin American countries (Brazil, Chile, Mexico, Uruguay, and Venezuela). In addition, the management of the disease can vary considerably, due to differences between countries in terms of the organization of health care services, including prevention, as well as in terms of socioeconomic status, as demonstrated by the differences among national guidelines.[3] This issue of the JBP presents three papers focused on the epidemiology, anthropometric characteristics, and management of COPD, as well as a campaign to improve knowledge of the disease, in Brazil.

Gonçalves-Macedo et al.[4] examined the temporal trends in COPD mortality rates in the various macro-regions of Brazil, together with the temporal trends in in-hospital morbidity and mortality. Their study highlights the fact that the perspective should be not only national but also regional. In fact, the authors found a downward temporal trend in COPD mortality rates in the macro-regions with higher socioeconomic indices, as well as downward temporal trends in the in-hospital morbidity rate and mortality indicators in all regions, those decreases being far more pronounced in the regions with optimal socioeconomic conditions. The most important finding of their study is that, despite the increase in COPD mortality rates observed between 2000 and 2016 in the northern, northeastern, and central-west regions, there was a significant reduction in the proportions of smokers in all regions in the same period, which underscores the importance of other factors, such as socioeconomic status, for mortality. How can programs aimed at improving disease management be planned and organized without this crucial information? In certain regions, campaigns aimed at reducing smoking habit will be appropriate, whereas in others an approach aimed at improving the socioeconomic status of patients with COPD is expected to be more beneficial.

Marchioro et al.,[5] on behalf of the PLATINO team, demonstrated anthropometric changes in individuals with COPD in the city of São Paulo, Brazil, between 2003 and 2012. In 2012, patients with mild COPD showed increases in their body mass index (BMI), whereas those with the more severe form of the disease (Global Initiative for Chronic Obstructive Lung Disease stage III or IV) showed an opposite trend. Those results, as emphasized by the authors, show the importance, at least in São Paulo but probably also in other cities and regions of Brazil, of knowing the nutritional profile of patients with COPD, in order to prevent not only weight loss, a well-known risk factor for mortality in COPD,[6] but also excessive weight gain, which is equally as dangerous, mainly in patients with the milder form of the disease.[7] Marchioro et al.[5] also showed that, in 2012, 60.3% of all patients with COPD in Brazil were overweight or obese. In a subanalysis of the PLATINO study, Montes de Oca et al.[8] found no significant difference in BMI strata among countries in South America. An international study conducted in eleven countries—Pakistan and ten countries in the Middle East and North Africa (MENA) region—known as the BREATHE study,[9] explored the prevalence of COPD symptoms, smoking habits, management of the disease, and disease burden, as well as reporting the rate of health care services utilization in the general population. In a subanalysis of that study, aimed at evaluating the BMI distribution among individuals with COPD, Koniski et al.[10] demonstrated a heterogeneous scenario, the proportion of patients with COPD with a BMI > 30 kg/m^2 (i.e., class II or III obesity) being highest in the Persian Gulf countries, whereas it was lowest in the Maghreb countries (Algeria, Morocco, Tunisia, Libya, and Mauritania) and Pakistan. Therefore, if the data are homogenous on a regional scale, taking a common approach to optimizing nutritional status appears to be a rational solution in South America, whereas not in other areas, such as the MENA region and Pakistan.

Finally, Alcântara et al.[11] evaluated the use of video lessons as a means of training a multidisciplinary primary health care team on COPD in the city of Goiânia, Brazil. In that "pilot" study, which involved only 36 participants (including community health agents, nurses, nursing assistants, physicians, and dentists), the authors

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demonstrated that a significant proportion of the participants (approximately 40%) had a low level of knowledge about COPD and showed that the video training program was a complete success, as evidenced by the fact that, after training, 100% of the participants expressed very strong agreement with all 16 items on the questionnaire employed, thus demonstrating optimal knowledge of the various aspects of the disease. In addition, the authors found that the levels of COPD knowledge were lowest among community health agents and nursing assistants, whereas they were highest among physicians. That information is valuable because, as discussed by the authors, various training strategies have been implemented in Brazil in an attempt to address the complexity of multidisciplinary primary health care. Such strategies cannot be irrespective of the specific target, given that physicians, nurses, and other members of the team will probably suggest different approaches based on their different backgrounds.

In conclusion, the optimization of COPD management requires the analysis of many factors, which can vary considerably across countries and regions. That is why there is an urgent need for local data, which are crucial to a better understanding of the scenario, as well as to the planning of campaigns aimed at improving disease management. Even if not everyone agrees with the saying "If you can't measure it, you can't improve it", there is no doubt that it is true in the field of COPD.

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Pulmonary rehabilitation: various diseases, many approaches, and multiple questions

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In 1605, Sir Francis Bacon said, "if a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties". Pulmonary rehabilitation has been recognized to improve dyspnea and quality of life since the 1960s; however, despite being such a well-established form of treatment, pulmonary rehabilitation still raises many questions.[1] Although pulmonary rehabilitation has become a well-established treatment for COPD, new evidence suggests that it can be used in other situations,[2] pulmonary rehabilitation having been reported to reduce mortality among pulmonary fibrosis patients undergoing single lung transplantation.[3]

In the current issue of the JBP, three articles demonstrate that pulmonary rehabilitation plays an important role in the treatment of chronic lung diseases, particularly COPD. In addition, the authors of the studies discuss the central role that physical exercise plays in the treatment of chronic lung diseases, as well as discussing how to implement exercise interventions and evaluate their outcomes. Although there is a body of evidence that pulmonary rehabilitation reduces dyspnea and exacerbations, as well as improving quality of life and exercise performance,[4] there is still controversy regarding the best model for exercise training. Although the six-minute walk test is the most widely used exercise test, it is a submaximal test that provides less detailed information than does ergospirometry. In the current issue of the JBP, Adolfo et al.[5] published a systematic review and meta-analysis of randomized studies, the objective of which was to compare high-intensity interval training and continuous training in terms of their effects on functional capacity and cardiovascular variables in patients with COPD. Of the 78 articles that were initially retrieved, only 6 were included in the meta-analysis, and all 6 were found to have a high risk of methodological bias. Although the authors found no difference between high-intensity interval training and continuous training or other interventions in terms of their effects on relative maximal oxygen consumption (VO_2), absolute maximal VO_2, and cardiovascular variables in COPD patients, the findings should be interpreted with caution because of their heterogeneity. Meta-analyses including methodologically flawed clinical studies can describe the current state of knowledge but cannot provide evidence upon which a given intervention can be based. Therefore, the question remains unanswered. Perrota et al.[6] evaluated the effects of a high-intensity rehabilitation program on ventilatory efficiency, i.e., the ratio of minute ventilation to carbon dioxide production (V_E/VCO_2) in 25 patients with COPD and stage I-IIIa non-small cell lung cancer undergoing rehabilitation three weeks before lobectomy. All of the patients had a peak VO_2 of 10-20 mL/kg per min or an FEV_1 of < 50% of predicted. Peak VO_2 and V_E/VCO_2 were found to have improved significantly after the rehabilitation program, showing that rehabilitation can improve ventilatory efficiency, improve aerobic capacity, and reduce postoperative risk, even in patients with severely impaired lung function. In addition, pulmonary rehabilitation was found to reduce dynamic hyperinflation and respiratory rate during exercise.[6] Although peak VO_2 during cardiopulmonary exercise testing is the best independent predictor of complications following pulmonary resection in patients with lung disease, ventilatory efficiency (V_E/VCO_2) during cardiopulmonary exercise testing has been shown to be an independent predictor of complications and mortality (in patients with a $V_E/VCO_2 > 35$).[7,8] Neder et al.[9] addressed the importance of ventilatory efficiency in patients with COPD, even in those with preserved lung function; in many cases, ventilatory efficiency can explain the discrepancy between dyspnea and lung function (FEV_1) and predict postoperative morbidity and mortality. In addition, the authors reported that pulmonary hypertension and heart failure can lead to an increase in V_E/VCO_2. Therefore, the use of ergospirometry before and after pulmonary rehabilitation can provide a deeper understanding of the outcomes to be evaluated. In fact, as the number of approaches increases, so does the number of questions. Pulmonary rehabilitation is a multidisciplinary program that addresses several aspects of the disease and underscores the importance of reversing physical deconditioning and understanding skeletal muscle issues. Mansour et al.[10] sought to establish cutoff points for clinical and functional variables for sarcopenia and dynapenia in 20 COPD patients who had moderate to very severe disease and skeletal muscle dysfunction and who were referred for pulmonary rehabilitation. Sarcopenia was diagnosed on the basis of skeletal muscle mass index (kg/m^2), as assessed by bioelectrical impedance analysis, whereas dynapenia was diagnosed on the basis of handgrip strength, as assessed with a hydraulic dynamometer. The major findings of the study[10] were that sarcopenia and dynapenia can be predicted by pulmonary function test results, respiratory muscle strength, and physical performance on the incremental shuttle walk test. Despite advances in the understanding of skeletal muscle

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dysfunction, there are currently no clear criteria or tools to define sarcopenia and dynapenia. According to the revised European consensus statement on the definition and diagnosis of sarcopenia,[11] some cutoff points for the diagnosis of sarcopenia are arbitrary, and the development of validated cutoff points will depend on normative data and their predictive value for hard endpoints. In addition, for height-dependent measures of sarcopenia (gait speed and muscle strength), studies are needed in order to establish whether gender- and region-specific thresholds can improve outcome prediction. Manini and Clark,[12] proponents of the term dynapenia, recognize that there is a lack of data to define cutoff points for dynapenia.

Despite the fact that there is ample evidence supporting the use of pulmonary rehabilitation regardless of its level of complexity, pulmonary rehabilitation continues to be a health care challenge. Many questions remain, and many components require better defined protocols and clearer measures that are relevant and feasible. In the meantime, we must live with our uncertainties and question everything, as Sir Francis Bacon would.

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Latent tuberculosis and the use of immunomodulatory agents

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Latent *Mycobacterium tuberculosis* infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of active tuberculosis.[1] The World Health Organization estimates that one fourth of the world population is infected with *M. tuberculosis*.[2] The main strategy for reducing the risk of developing the disease in individuals infected with *M. tuberculosis*, who are at increased risk of progression to active tuberculosis, is LTBI treatment,[1] which is able to reduce this risk by 60-90%[3] and is one of the main components of the World Health Organization's End TB strategy.[4]

Between 5% and 10% of individuals with LTBI will progress to active tuberculosis in their lifetime, most within the first 5 years after infection.[5] The remainder of infected individuals will be able to contain the infection through an effective cellular immune response, which is dynamic.[6] The greatest risk factor for progression to active tuberculosis is poor immune status.[7] Therefore, HIV-infected individuals are at increased risk of progression to active tuberculosis, as are patients with chronic renal failure, patients with silicosis, and patients on immunosuppressive therapy.

TNF is a pro-inflammatory cytokine that plays an essential role in containing mycobacterial infection. TNF-α is initially produced by macrophages and monocytes activated by various stimuli, including viral and bacterial infections.[8] The release of TNF-α in response to mycobacterial infection increases phagocytosis and killing of mycobacteria,[9] and its production is required for the formation of granulomas, which engulf mycobacteria and prevent their proliferation.[10] In addition, TNF-α helps control mycobacterial infection by inducing apoptosis of ineffective macrophages, thus preventing these cells from becoming intracellular sanctuaries.[10]

The treatment of rheumatic diseases has undergone a drastic transformation since the introduction of biological agents, which are able to reduce the inflammatory process and inhibit progressive structural damage.[11] TNF inhibitors are biological agents that reduce inflammation and are able to modify the progression of chronic inflammatory diseases by inhibiting TNF-α. Despite the numerous benefits of using these agents in this population, the development of active tuberculosis should be expected when any biological agent with anti-TNF activity is used.[6] Therefore, screening for and treatment of LTBI are recommended in patients with chronic inflammatory diseases for which treatment with anti-TNF biological agents is indicated.

In this issue of the JBP, Lopes et al.[12] provide information on the risk of developing tuberculosis in patients with LTBI receiving immunomodulators and anti-TNF biological agents. The authors followed patients with chronic inflammatory diseases and LTBI, the mean follow-up period being 3 years (range, 6 months to 4 years). In the study, treatment with biological agents and other immunomodulators was initiated no sooner than 1 month after initiation of isoniazid therapy. There were only 6 cases of active tuberculosis among 101 patients with LTBI. The risk of developing tuberculosis was 1.39 times higher in patients treated with biological agents than in those treated with other immunosuppressants (although the statistical significance of this estimate was not confirmed, possibly because of the small number of active tuberculosis cases). In addition, the patients who developed active tuberculosis were diagnosed with the disease 10 months after the initiation of biological therapy. A history of contact with a tuberculosis case was strongly associated with the development of tuberculosis, which demonstrates that recently acquired infection is a risk factor for the development of active tuberculosis.[5] The most commonly used biological agent, prescribed in 58% of the cases, was infliximab. Of the 5 patients who developed tuberculosis while on biological agents, 4 used infliximab, which is described in the literature as the biological agent that poses the greatest risk of development of active tuberculosis.[6]

Another very interesting result of the study was the high LTBI treatment completion rate.[12] LTBI treatment with isoniazid was offered as a way to reduce the risk of developing tuberculosis in patients with a positive tuberculin skin test result and no signs or symptoms of active tuberculosis. More than 95% of the patients completed the treatment. The authors reported only one case of treatment abandonment, which is an excellent result, given that LTBI treatment abandonment is the most commonly reported reason for treatment failure. In addition, the low incidence of adverse effects in the study population, which caused treatment discontinuation in only 4% of the cases, is of note.

These results, found at a referral facility, underscore the need to screen patients who are referred for immunosuppressive therapy for LTBI and to offer LTBI treatment, which proved to be safe and for which the adherence rate was high in patients with chronic inflammatory diseases. Nevertheless, monitoring for tuberculosis symptoms is required throughout the period of treatment with biological agents, particularly in patients who need to be on immunosuppressants for more than 9 months.

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Mosaic attenuation

Edson Marchiori[1,a], Bruno Hochhegger[2,b], Gláucia Zanetti[1,c]

A 48-year-old woman presented with a 1-year history of tiredness, progressive dyspnea, dry cough, and weight loss (16 kg in 1 year). Laboratory test results were normal. Chest CT revealed a mosaic attenuation pattern (MAP; Figure 1).

Chest CT scans basically show the MAP. By definition, mosaic attenuation is a CT pattern in which areas of differing attenuation are found diffusely distributed throughout the lung parenchyma. These areas have well-defined borders, which correspond to the borders of the secondary pulmonary lobules or to a set of them. An MAP may be due to vascular diseases, small airways diseases, and parenchymal diseases.[1]

The main example of vascular disease causing an MAP is pulmonary hypertension due to chronic pulmonary thromboembolism. In such cases, the areas of hypoattenuation correspond to hypoperfusion zones, and the areas of hyperattenuation correspond to zones with normal vascularization or increased perfusion. Signs of chronic thromboembolism that can aid in diagnosis include filling defects in the pulmonary arteries, serpiginous pulmonary arteries, and bronchial artery hypertrophy. Another important sign is flow redistribution, with more pronounced vascularization in the hyperattenuated areas and hypoflow in the hypoattenuated areas. Signs of pulmonary hypertension, such as right ventricular enlargement, interventricular septal bowing, and pulmonary artery dilatation, may also be present.

Parenchymal involvement characterized by sparse areas of ground-glass attenuation can be seen in various diseases, such as pulmonary hemorrhage, *Pneumocystis jirovecii* pneumonia, and alveolar proteinosis. In such cases, the abnormal parenchyma corresponds to the denser zones, which show ground-glass attenuation, and the less dense zones correspond to the normal parenchyma. The presence of interlobular septal thickening reinforces this possibility.

The main small airways diseases that can present with an MAP are bronchiolitis (including hypersensitivity pneumonitis)[2] and bronchial asthma. In such cases, there is basically air trapping, with the lower density zones corresponding to the abnormal areas, where the air is trapped as a result of partial bronchial or bronchiolar obstruction. These areas are best shown on serial CT scans obtained during expiration. Frequently, bronchial wall thickening is also observed, with or without dilatation or mucous plugs. The number and caliber of vessels may decrease as a result of hypoxic vasoconstriction.

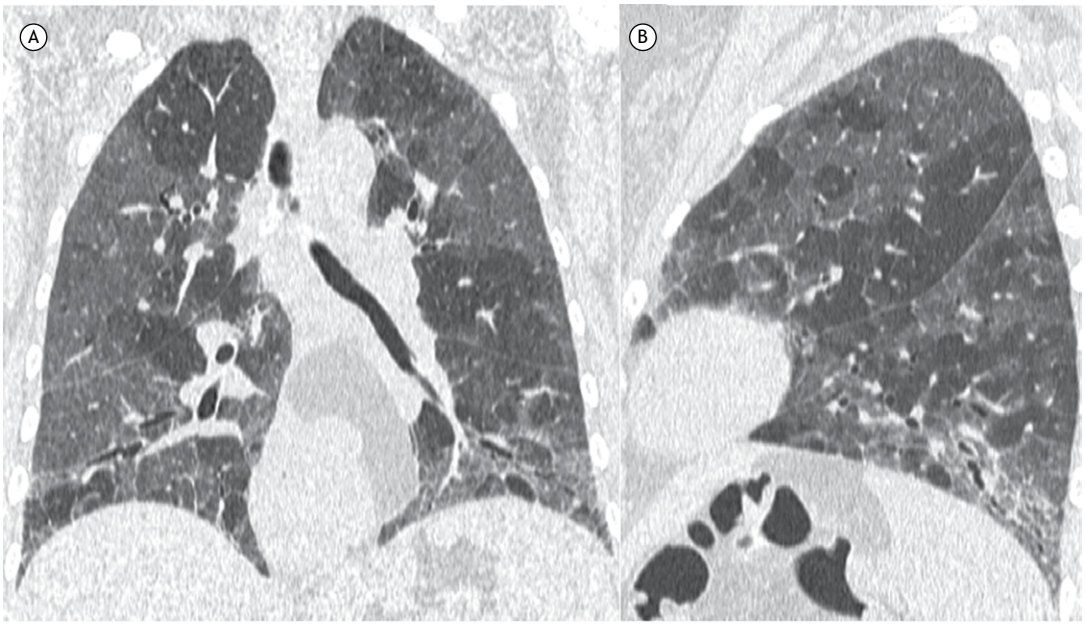

Figure 1. Coronal and sagittal chest CT reconstructions (A and B, respectively) showing areas of differing attenuation in the lung parenchyma. Slices obtained during expiration (not shown) revealed air trapping. Also note reticular opacities and bronchiolectasis at the lung bases.

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Therefore, in practical terms, the aforementioned causes can be differentiated on CT by taking two major factors in consideration: the presence or absence of air trapping; and the evaluation of the pattern of pulmonary vascularization. Our patient did not present with changes in pulmonary vascularization or in arterial blood flow redistribution, but there was air trapping; therefore, she was classified as having small airways impairment. She had a history of sleeping in a room with more than twenty bird cages. The final diagnosis was hypersensitivity pneumonitis.

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Number needed to treat: a useful statistic to evaluate the impact of an intervention

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PRACTICAL SCENARIO

A meta-analysis examined the effect of the use of daily medium-dose inhaled corticosteroids (ICS) on preventing exacerbations among preschoolers with recurrent wheeze. It summarized the results of 15 randomized clinical trials (RCTs) involving 3,278 individuals that showed that the use of daily ICS, compared with that of placebo, prevented exacerbations by 30% [risk ratio (RR) = 0.70; 95% CI: 0.61-0.79; number needed to treat (NNT) = 9].[1]

COMPARING RISKS

The impact of interventions can be estimated by comparing the incidence of the outcome (e.g., exacerbations) in the experimental group vs. a control group (e.g., placebo) by calculating an outcome ratio or difference across the intervention groups. The typical ratio calculated is the risk in the intervention group over the risk in the control group, designated the risk ratio (RR). In RCTs, the difference in risk between groups is called the absolute risk reduction (ARR), and it represents the proportion of outcomes reduced by the new intervention to the comparison group. Similar estimates can be calculated in observational studies replacing an intervention with the exposure of interest; for example, tobacco smokers compared with nonsmokers when reporting the risk of tobacco-related disease.

A statistic related to the ARR is the NNT, which is important because it provides an estimate of the number of patients that are required to be treated to avoid one additional patient from developing the outcome of interest (Table 1).[2]

The popularity of NNT has increased considerably, although this statistic is not necessarily easier to grasp than the ARR, either by patients or physicians. It is useful to remember that the lower the NNT, the higher the effectiveness of the intervention. In our example, an NNT of 9 is interpreted as follows: 9 children, on average, need to be treated with ICS to prevent 1 additional child from having an exacerbation.

More recently, RCTs also evaluate the impact of adverse events of an intervention by reporting the number needed to harm (NNH) in addition to the NNT. NNH is defined as the average number of individuals that would need to be exposed to a new intervention to produce one additional adverse outcome.

LIMITATIONS AND KEY POINTS

The reporting of NNT and NNH should always include confidence intervals and not only a point estimate.

The importance of taking into account the baseline risk to properly assess an intervention in an RCT cannot be overemphasized. Table 1 shows that as the incidence of the outcome in the control group increases, an identical RR results in greater ARRs and, consequently, lower NNT. Therefore, the effect can be exaggerated by simply reporting an RR of 0.75. In both examples, the risk is reduced by 25%, but NNT informs how many individuals must be treated in order to decrease that risk or absolute difference. It is recommended reporting both absolute and relative effect sizes.

The size and clinical impact of the effect of the intervention are important. Similar RCTs may have the same NNT, but their clinical relevance is different if the NNT refers to preventing one death or one COPD exacerbation when compared with preventing a small decrease in FEV_1 or another surrogate outcome.

Table 1. Comparing risks and interpreting results across different clinical scenarios. RR: risk ratio; ARR: absolute risk reduction; and NNT: number needed to treat.[2]

	Result	Interpretation
Low baseline risk (20% risk of death in the control group)		
Control group: n = 500; 100 (20%) deaths; Intervention group: n = 500; 75 (15%) deaths		
RR	15%/20% = 0.75	The intervention reduces risk **by** 25%
ARR	20% − 15% = 5%	The intervention reduces risk **in** 5%
NNT	1/5% =20	20 patients need to receive the intervention to prevent 1 death
High baseline risk (50% risk of death in the control group)		
Control group: n = 500; 250 (50%) deaths; Intervention group: n = 500; 188 (38%) deaths		
RR	38%/50% = 0.75	The intervention reduces risk **by** 25%
ARR	50% − 38% =12%	The intervention reduces risk **in** 12%
NNT	1/12% = 8	8 patients need to receive the intervention to prevent 1 death

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The importance of appropriate reference values in patients suspected of having obstructive lung disease

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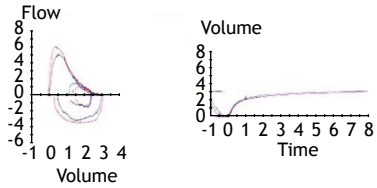
CLINICAL SCENARIO

A 69-year-old White female patient was suspected of having COPD and was therefore referred for functional evaluation. She reported a 4-year history of morning cough and sputum production, as well as dyspnea when hurrying on level ground or walking up a slight incline. She reported no wheezing attacks. The patient was a former

Spirometry		Pre	Ref		Ref	% Ref	Post	% Chg
FVC	Liters	3.02	2.78	(2.0 - 3.5)	109	3.11	112	3
FEV_1	Liters	2.08	2.16	(1.6 - 2.7)	96	2.19	101	6
FEV_1/FVC	%	69	78	(65.2 - 91.5)		71		
FEV_1/SVC	%	67				69		
$FEF_{25-75\%}$	L/sec	1.24	1.87	(0.9 - 2.9)	66	1.42	76	15
$FEF_{75-85\%}$	L/sec	0.25				0.34		33
$FEF_{50\%}$	L/sec	2.23				2.12		-5
$FEF_{75\%}$	L/sec	0.39	0.46	(0.2- 0.8)	85	0.54	117	38
PEF	L/sec	5.03				6.04		20
$FET_{25-75\%}$	Sec	1.22				1.11		-9
Vol Extrap	Liters	0.10				0.03		-70

Spirometry		Pre	Ref		Ref	% Ref	Post	% Chg
FVC	Liters	3.02	2.90	(2.3 - 3.5)	104	3.11	107	3
FEV_1	Liters	2.08	2.27	(1.7 - 2.9)	91	2.19	97	6
FEV_1/FVC	%	69	78	(69.7 - 86.7)		71		
FEV_1/SVC	%	67				69		
$FEF_{25-75\%}$	L/sec	1.24	2.06	(1.2 - 2.9)	60	1.42	69	15
$FEF_{75-85\%}$	L/sec	0.25	0.42	(0.2 - 0.6)	61	0.34	80	33
$FEF_{50\%}$	L/sec	2.23	2.79	(1.6 - 4.0)	80	2.12	76	-5
$FEF_{75\%}$	L/sec	0.39	0.68	(0.4 - 1.0)	57	0.54	79	38
PEF	L/sec	5.03	6.86	(5.1 - 8.6)	73	6.04	88	20
$FET_{25-75\%}$	Sec	1.22	0.81	(0.5 - 1.1)	150	1.11	136	-9
Vol Extrap	Liters	0.10				0.03		-70



Lung Volumes		Pre	Ref		Ref	% Ref	Post	% Chg
TLC	Liters	6.06	4.92	(4.2 - 5.7)	123	5.93	121	-2
VC	Liters	3.12	2.90	(2.3 - 3.5)	107	3.19	110	2
IC	Liters	2.97	2.31		103	2.54	110	7
FRC PL	Liters	3.69	2.55	(1.8 - 3.3)	145	3.39	133	-8
ERV	Liters	0.47	0.74		64	0.46	61	-4
RV	Liters	2.95	1.93	(1.3 - 2.6)	152	2.75	142	-7
RV/TLC	%	49	39	(29.5 - 49.3)		46		
Vtg	Liters	4.22				3.78		-10
Resistance								
sRaw	$cmH_2O/L/s/L$	10.57	5.95	(3.9 - 8.0)	178	7.04	118	-33
sGaw	$L/s/cmH_2O/L$	0.095	0.168	(0.1 - 0.2)	56	0.142	85	50

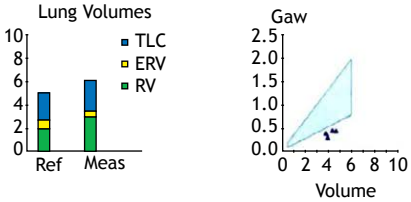


Figure 1. Functional values in patients suspected of having COPD, in comparison with the predicted values suggested by the Global Lung Function Initiative (in A)[1] and the predicted values for spirometry and lung volumes in the Brazilian population (in B and C).[2]

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smoker (with a smoking history of 35 pack-years), and her body mass index was 27.3 kg/m^2.

FUNCTIONAL ASSESSMENT

The patient underwent spirometry, which was performed in accordance with acceptability and reproducibility criteria. Spirometry results and lung volumes were determined on the basis of reference values suggested by the Global Lung Function Initiative (GLI) in 2012[1] and reference values for the Brazilian population,[2] and are shown in Figure 1.

When the GLI reference values were used,[1] the FEV_1/FVC ratio, $FEF_{25-75\%}$, and $FEF_{75\%}$ were found to be within the predicted range. When the reference equations for the Brazilian population were used,[2] the FEV_1/FVC ratio and $FEF_{75\%}$ were found to be slightly reduced. The presence of airflow obstruction was confirmed by increased specific airway resistance, RV, and TLC. There were no significant changes in lung function parameters after administration of 400 µg of bronchodilator via a metered dose inhaler.

COMMENTARY

In order to interpret pulmonary function test results correctly, it is critical to use appropriate reference values. Because numerous predicted value equations are available in the literature, reference values vary widely.

The GLI equations[1] included a large number of individuals from many centers. The results obtained were influenced by several factors, including sample selection and the variety of measurement and quality control techniques, all of which made it difficult to aggregate the results across studies and increased the range of predicted values, with very low lower limits. For example, for a 65-year-old male who is 170 cm in height, the lower limit of normal is 0.70 when the reference values for the Brazilian population are used[2] and 0.65 when the GLI reference values are used.[1] For a 65-year-old female who is 165 cm in height, the lower limit of normal is 0.70 when the reference values for the Brazilian population are used[2] and 0.66 when the GLI reference values are used.[3] The Global Initiative for Chronic Obstructive Lung Disease maintains that airflow obstruction should be defined by an FEV_1/FVC ratio of < 0.70; not surprisingly, a recent study[4] found that an FEV_1/FVC ratio of < 0.70 had better predictive value for long-term COPD-related hospitalization and mortality than did the lower limit of normal as defined by the GLI reference equations (i.e., < 0.70 for middle-aged individuals and the elderly).

The same applies to the lower limits of normal for $FEF_{25-75\%}$ and $FEF_{75\%}$, mid- and end-expiratory flows being of no value in characterizing airflow limitation when the limits recommended by the GLI[1] are used.[5]

In the study conducted in Brazil,[2] a small number of certified technicians supervised by the principal investigator throughout the study performed all tests at eight selected centers. Extensive efforts were made to meet acceptability and reproducibility criteria. In that study,[2] in addition to FEV_1 and $FVC < 0.15$ L, at least three peak flow values lower than the highest value by $< 10\%$ were required for acceptability. These criteria had not been used in previous studies.

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Anthropometric status of individuals with COPD in the city of São Paulo, Brazil, over time - analysis of a population-based study

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ABSTRACT

Objective: To evaluate the anthropometric data obtained for residents of the city of São Paulo, Brazil, in a study of Latin America conducted in two phases (baseline, in 2003, and follow-up, in 2012). **Methods:** This was an analysis of data obtained for São Paulo residents in a two-phase population-based study evaluating the prevalence of COPD and its relationship with certain risk factors among individuals ≥ 40 years of age. The anthropometric data included values for weight, height, body mass index (BMI), and waist circumference. In the follow-up phase of that study, the same variables were evaluated in the same population sample as that of the baseline phase. **Results:** Of the 1,000 São Paulo residents enrolled in the baseline phase of that study, 587 participated in the follow-up phase, and 80 (13.6%) of those 587 subjects had COPD. Comparing the baseline and follow-up phases, we found increases in all anthropometric measures in both groups (COPD and non-COPD), although the differences were significant only in the non-COPD group. The subjects with mild COPD showed increases in weight and BMI (Δweight = 1.6 ± 5.7 and ΔBMI = 0.7 ± 2.2), whereas those with moderate or severe COPD showed reductions (Δweight = −1.7 ± 8.1 and ΔBMI = −0.4 ± 3.0), as did those with severe or very severe COPD (Δweight = −0.5 ± 5.4 and ΔBMI = −0.8 ± 3.3). **Conclusions:** Between the two phases of the study, the subjects with mild COPD showed increases in weight and BMI, whereas those with a more severe form of the disease showed reductions.

Keywords: Pulmonary disease, chronic obstructive; Body mass index; Obesity; Waist circumference.

INTRODUCTION

One of the diseases with the highest mortality rates in the world, COPD is projected to rank 3rd among the leading causes of death worldwide by 2020.[1] The prevalence of COPD in the city of São Paulo, Brazil, in 2003, according to the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study, was 15.8% of the population ≥ 40 years of age.[2]

Currently, the inflammatory component of COPD is believed not only to cause injury to the lungs but also to have a systemic effect, being associated with several morbidities, such as loss of lean body mass and muscle dysfunction.[3] Malnutrition is one of the major systemic manifestations of COPD and is usually due to loss of mean body mass accompanied by weight loss.[4] Muscle depletion is typically multifactorial, including an increased basal metabolic rate, reduced caloric intake, senile sarcopenia, inactivity,[5,6] systemic inflammatory activity, hormonal changes, and chronic use of systemic corticosteroids.[7,8]

It has been established that a low body mass index (BMI), as well as a low lean body mass index, is associated with a worse prognosis, a higher risk of exacerbations, reduced exercise capacity, and reduced quality of life in individuals with COPD.[9-11]

At the other end of the spectrum, the number of overweight or obese people is known to have increased in recent decades, obesity being considered a global epidemic.[12] In Brazil, according to data from a telephone survey conducted by the Brazilian National Ministry of Health, the frequency of overweight was 52.5% in 2014.[13] Therefore, since COPD affects the same age group in which obesity tends to increase, the association between COPD and obesity is expected to be prevalent. In addition, knowing that cardiovascular disease (a condition for which the major risk factor is being overweight) is the leading cause of death in COPD patients, the association between COPD and obesity is expected to have a great impact on patient prognosis.[3]

Analysis of the nutritional status of COPD patients over time is essential to the follow-up of such patients. Weight loss in COPD patients has been shown to be an independent risk factor for mortality.[14,15] However, to date, we know of no studies conducted in Brazil that have evaluated weight change in COPD patients.

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The objective of the present study was to evaluate the anthropometric status of COPD patients in the greater metropolitan area of São Paulo over time by using baseline and follow-up data from the PLATINO study (a population-based study), and to compare the anthropometric status of individuals with and without COPD.

METHODS

The detailed design of the PLATINO study has been published elsewhere.[16] In brief, in 2003, the study known as the PLATINO baseline study aimed to describe the epidemiology of COPD in five cities in Latin America: São Paulo, Santiago, Mexico City, Montevideo, and Caracas. Those cities were divided into socioeconomic level census tracts. Through systematic sampling, approximately 15 households were visited and all residents ≥ 40 years of age were invited to participate in the study. In 2012, the study known as the PLATINO follow-up study was conducted with the same subjects as before and using the same questionnaires. All interviews and tests, including pre- and post-bronchodilator spirometry, occurred in the participants' own homes. Anthropometric assessments included the measurement of height (portable stadiometer—Sanny; American Medical do Brasil Ltda., São Bernardo do Campo, Brazil); weight (electronic scale—Techline®, Taiwan); and waist circumference (WC; Fiberglass®, Brazil); as well as the calculation of BMI (kg/m^2). The WC measurement was made at the level of the umbilicus, at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest.[17] The BMI cut-off points for nutritional status in individuals ≤ 59 years of age were those proposed by the World Health Organization[12]: BMI < 18.5 kg/m^2 (underweight); BMI ≥ 18.5 kg/m^2 and < 25.0 kg/m^2 (normal weight); BMI ≥ 25.0 kg/m^2 and < 30.0 kg/m^2 (overweight); and BMI ≥ 30.0 kg/m^2 (obese). For individuals > 59 years of age, the BMI cut-off points were those proposed by the Pan American Health Organization[18]: BMI ≤ 23 kg/m^2 (underweight); BMI > 23 kg/m^2 and < 28 kg/m^2 (normal weight); BMI ≥ 28 kg/m^2 and < 30 kg/m^2 (overweight); and BMI ≥ 30 kg/m^2 (obesity). Normal WC was defined as WC < 80 cm for women and WC < 94 cm for men.[17] All anthropometric variables were assessed in the PLATINO baseline and follow-up studies, and were compared as absolute values and percent changes. All spirometry tests and their quality assessment were performed in accordance with the American Thoracic Society 2005 recommendations.[19] Predicted values for the spirometric variables were calculated with an equation developed for the Latin-American population.[20]

Baseline participants who were successfully contacted and declined to participate in the follow-up phase of the PLATINO study completed a shortened questionnaire with questions identical to those used in the baseline phase. Participants who developed a mental illness during the follow-up period were excluded. The exclusion criteria for undergoing spirometry are described in detail in the PLATINO baseline study.[16]

The study project was approved by the Research Ethics Committee of the Federal University of São Paulo, and all participants gave written informed consent before any intervention, in both phases of the PLATINO study.

Statistical analysis

Numerical data are expressed as means and standard deviations. Categorical data are presented as absolute numbers and proportions. Comparison of mean numerical variables between two independent groups was performed using the Student's t-test. For comparison of means between two groups at different time points, repeated measures analysis was performed using a general linear model to compare the groups (COPD and non-COPD) and time point interaction analysis at two time points (PLATINO baseline and follow-up studies) plus the Bonferroni post hoc test. For comparison of numerical data among three or more groups, ANOVA and the Bonferroni post hoc test were used. Comparison of proportions of categorical variables between two independent groups was performed using the chi-square test. McNemar's test was used to compare categorical data for the same group at different time points (nutritional status at the time of the PLATINO baseline and follow-up studies). The level of significance was set at 5%. Statistical analyses were performed with the Statistical Package for the Social Sciences, version 10.0 (SPSS Inc., Chicago, IL, USA) and Stata, version 8.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Of the 1,000 participants in the PLATINO baseline study in the city of São Paulo, Brazil, 944 were successfully contacted. Of those, 135 had died, 141 declined to participate in the follow-up, and 55 were lost to that follow-up. Therefore, interviews were performed with 613 individuals, of whom 594 underwent pre- and post-bronchodilator spirometry and 587 underwent anthropometric assessment.

Table 1 presents the demographic data for the total sample and by group (non-COPD and COPD). The mean age was higher in the COPD group than in the non-COPD group ($p < 0.001$). The two groups were similar with respect to gender and anthropometric data (weight, height, WC, and BMI). Despite being low overall, smoking history was greater in the COPD group ($p < 0.05$). As expected, FEV_1 and the FEV_1/FVC ratio were significantly lower in the COPD group.

Figure 1 (A, B, and C) presents a comparison of the results of the PLATINO baseline study and those of the PLATINO follow-up study with regard to weight, BMI, and WC in the non-COPD and COPD groups. General linear model analysis for the baseline phase revealed that there were no statistically significant differences in those variables between the COPD and non-COPD groups. Weight and BMI were found to have increased

Table 1. Demographic data on participants in the follow-up phase of the Latin American Project for the Investigation of Obstructive Lung Disease study in the city of São Paulo, Brazil.[a]

Data	Groups		
	Total (N = 587)	Non-COPD (n = 507)	COPD (n = 80)
Age, years	53.3 ± 9.6	52.5 ± 9.3	58.1 ± 10.0**
Gender			
Male	262 (44.6)	223 (44.0)	39 (48.8)
Female	325 (55.4)	284 (56.0)	41 (51.2)
Height, m	1.60 ± 0.10	1.60 ± 0.94	1.58 ± 0.15
Weight, kg	72.3 ± 15.6	72.6 ± 15.0	69.7 ± 18.5
Waist circumference, cm	97.7 ± 13.3	97.6 ± 12.9	97.7 ± 15.6
BMI, kg/m^2	28.4 ± 8.1	28.3 ± 5.4	27.2 ± 6.7
Smoking history, pack-years	5.7 ± 12.0	5.2 ± 11.5	8.8 ± 14.7*
Post-BD FEV_1/FVC	0.79 ± 0.08	0.81 ± 0.05	0.63 ± 0.06
Post-BD FEV_1/FVC, % of predicted	98.95 ± 10.1	101.8 ± 6.5	81.0 ± 8.4**
Post-BD FEV_1, L	2.73 ± 0.75	2.81 ± 0.73	2.23 ± 0.73
Post-BD FEV_1, % of predicted	98.50 ± 17.0	100.8 ± 15.7	84.0 ± 18.3**
Post-BD FVC, L	3.48 ± 0.92	3.47 ± 0.89	3.51 ± 1.08
Post-BD CVF, % of predicted	99.20 ± 16.2	98.5 ± 15.2	103.3 ± 21.4#

BMI: body mass index; and post-BD: post-bronchodilator. [a]Values expressed as n (%) or as mean ± SD. #p < 0.016. *p < 0.05. **p < 0.001.

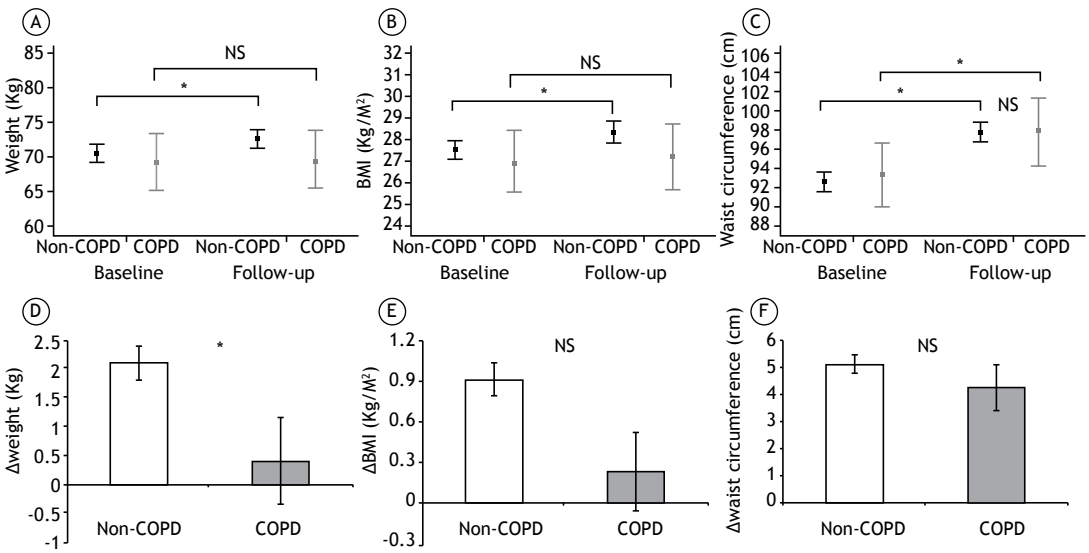

Figure 1. Comparison of mean weight, body mass index (BMI), and waist circumference - and their 95% CIs - in the baseline and follow-up phases of the Latin American Project for the Investigation of Obstructive Lung Disease study in the city of São Paulo, Brazil, between the COPD and non-COPD groups (in A, B, and C, respectively), as well as of mean changes in weight, BMI, and waist circumference between those groups (in D, E, and F, respectively). NS: not significant. *p < 0.05.

significantly only in the non-COPD group (p < 0.005). However, WC increased significantly in both groups (p < 0.005). Comparison of weight, BMI, and WC for the follow-up phase revealed no statistically significant differences between the two groups. Figures 1D, 1E, and 1F show comparisons of changes in weight, BMI, and WC, respectively, between the two groups in the follow-up phase. The non-COPD group had a weight gain of approximately 2 kg, whereas the COPD group had a weight gain of about 0.4 kg (p = 0.042). As a result of the difference in weight change, the BMI increase was also smaller in the COPD group compared with the non-COPD group (0.23 kg/m^2 vs. 0.90 kg/m^2), although no statistically significant difference was found (p = 0.054). There was no statistically significantly difference in WC change between the COPD and non-COPD groups.

Figure 2 presents the distribution of the individuals in the non-COPD and COPD groups by nutritional status. In both groups, normal BMIs predominated in the baseline phase. In the non-COPD group, there was a reduction in the proportion of normal weight

individuals and a more significant increase in the proportion of overweight and obese individuals ($p < 0.005$). In the COPD group, however, the change in classification was not statistically significant.

Table 2 shows changes in nutritional status from the baseline to the follow-up phase of the PLATINO study in the non-COPD and COPD groups, by BMI stratification. The interesting thing about this table is that we can analyze and compare the nutritional status of the participants in the two phases. In the non-COPD group, there was always an increase in the number of individuals who had lower BMIs in the baseline phase and higher BMIs in the follow-up phase, that is, who had a greater weight gain. For example, of the individuals who had normal nutritional status in the baseline phase, 66.1% remained in the same classification, whereas 21.0% and 3.2% were reclassified as overweight and obese, respectively. Those changes also occurred in the underweight and overweight individuals and were statistically significant. In contrast, the patients in the COPD group did not experience the same changes as those seen in individuals without COPD. The vast majority of the COPD patients who were underweight in the baseline phase remained in the same classification (91.7%). A small proportion of the COPD patients who were normal weight or overweight were reclassified as being in higher weight categories (7.0% and 16.7%, respectively). An important point is that, of the COPD patients who were overweight, 50% were reclassified as normal weight, but there was no statistically significant difference. This demonstrates that the COPD patients tended not to gain weight in the long run.

Table 3 compares changes in nutritional parameters from the baseline to the follow-up phase in the non-COPD group and in the COPD group subdivided according to disease severity (degree of obstruction) as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1] The patients with moderate, severe, and very severe COPD (GOLD stage II-III-IV) showed reductions in weight and BMI, unlike the individuals in the non-COPD group and those with GOLD stage I COPD, who showed increases. Post hoc analysis revealed that weight change was statistically significantly different between the non-COPD group and the GOLD stage II COPD subgroup, either in absolute ($p = 0.03$) or relative ($p = 0.054$) values. The proportional change in BMI was also significant ($p = 0.023$), with the non-COPD group showing the greatest gain in BMI (mean = 9.6%). However, WC increased in all groups, with no statistically significant differences among the disease severity subgroups or in relation to the non-COPD group (Table 3).

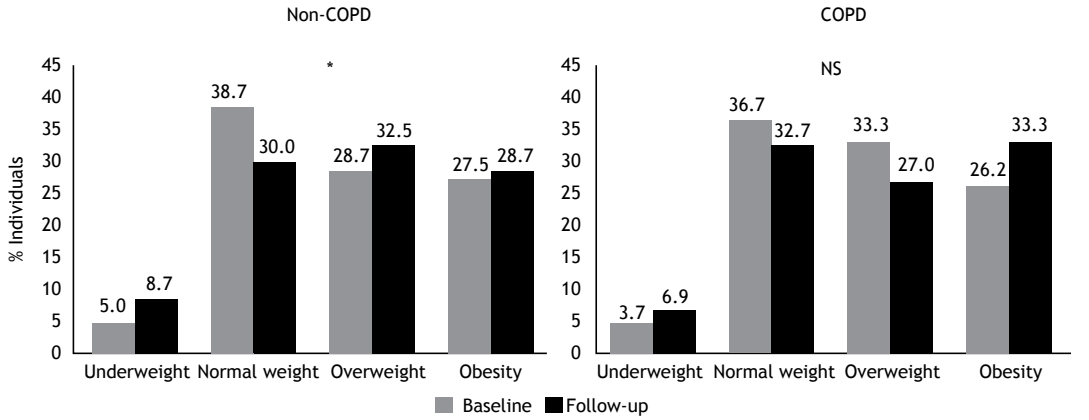

Figure 2. Nutritional status of individuals in the non-COPD and COPD groups in the baseline and follow-up phases of the Latin American Project for the Investigation of Obstructive Lung Disease study in the city of São Paulo, Brazil. NS: not significant.

Table 2. Change in nutritional status, by BMI, from the baseline to the follow-up phase of the Latin American Project for the Investigation of Obstructive Lung Disease study in the city of São Paulo, Brazil, in the COPD and non-COPD groups.

		Follow-up									
		Non-COPD					COPD				
		Underweight	Normal weight	Overweight	Obesity	p	Underweight	Normal weight	Overweight	Obesity	p
Baseline	Underweight	14 (73.7)	5 (26.3)	-	-	< 0.001	11 (91.7)	1 (8.3)	-	-	NS
	Normal weight	18 (9.7)	123 (66.1)	39 (21)	6 (3.2)		5 (17. 9)	20 (71.4)	1 (3.6)	1 (3.4)	
	Overweight	3 (1.8)	35 (20.7)	81 (47.9)	50 (29.6)		-	9 (50)	6 (33.3)	3 (16.7)	
	Obesity	-	3 (2. 3)	17 (12.8)	113 (85)		-	1 (4.5)	3 (13.6)	18 (81.8)	

NS: not significant. [a]Values expressed as n (%).

Analysis of WC over time revealed that, in the baseline phase, 67% of the individuals without COPD and 62% of the individuals with COPD already had an increased WC. It also showed that, in the follow-up phase, individuals with an increased WC continued to predominate in the non-COPD and COPD groups (81.5% vs. 72.0%; Figure 3).

DISCUSSION

Our findings showed that there were no significant changes in weight, BMI, or WC in the COPD group at 9 years from baseline. In addition, the individuals in the COPD group gained less weight than did those in the non-COPD group. There was an increase in the proportions of overweight and obese individuals, and those proportions were significantly higher in the non-COPD group than in the COPD group. Similarly, there was a greater WC gain in the non-COPD group, as well as a higher proportion of individuals with increased WC values, in the follow-up phase.

Our study showed that the prevalence rates for overweight and obesity were high in the COPD and non-COPD groups in the two phases of the PLATINO study. In the non-COPD group, the prevalence rates for excess weight (overweight and obesity) were 56.2% and 61.2% in the baseline and follow-up phases, respectively, whereas in the COPD group, they were 59.5% and 60.3%, respectively. In line with these findings, some studies have shown that the prevalence rates for excess weight in COPD patients are high, being similar to or higher than those seen in healthy individuals in the same age group.[21,22] The prevalence of excess weight in COPD patients varies by population studied—23% in South America.[23] Therefore, our data underscore the idea that obesity is a global epidemic and occurs concomitantly with several morbidities. Although the objective of the present study was to evaluate anthropometric parameters over time, the results of the PLATINO baseline and follow-up studies give us an idea of the prevalence of the obesity-COPD association in Brazil, which had not been evaluated in population-based studies. Some factors can explain the possible causes of this common association. In addition to a systemic inflammatory state, common to both morbidities,[24] the risk of obesity in COPD patients increases as a result of their sedentary lifestyle, given that they have poor physical capacity.[25]

The prognostic value of nutritional status in COPD is well established. A reduced BMI is associated with an increase in all-cause mortality, regardless of the degree of obstruction.[26] Recent studies indicate that lean body mass index is an even more important prognostic determinant than BMI in patients with moderate to severe disease.[27,28] It is of note that the relative risk of death seems to decrease with excess weight (overweight and obesity) in patients with GOLD stage III and IV COPD, whereas it increases in those with GOLD stage I and II COPD.[26] This association between obesity and paradoxical improvement in prognosis is present in several chronic diseases, such as congestive heart failure, chronic renal failure, and rheumatoid arthritis.[29] Contrary to this apparent benefit of excess weight for COPD patients, cardiovascular risk is known to be high in COPD, regardless of BMI.[30] Therefore, if we add to this the cardiovascular risks associated with obesity, there is a high risk of atherosclerotic disease in this population.[31]

In our sample, the patients with mild disease (GOLD stage I) gained weight and showed increases in BMI over time, whereas those with advanced stage disease (GOLD stage II-III-IV) showed reductions in weight and BMI. As in our study, Eisner et al.[22] reported a high

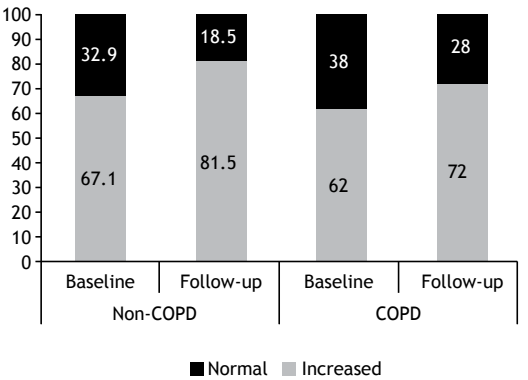

Figure 3. Waist circumference status in the non-COPD and COPD groups in the baseline and follow-up phases of the Latin American Project for the Investigation of Obstructive Lung Disease study in the city of São Paulo, Brazil.

Table 3. Change in nutritional parameters vs. COPD staging as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[a]

Parameter	Non-COPD	GOLD			p
		I	II	III and IV	
	(n = 508)	(n = 50)	(n = 26)	(n = 4)	
Δweight, kg	2.1 ± 6.8	1.6 ± 5.7	−1.7 ± 8.1*	−0.5 ± 5.4	0.04
Δweight, %	3.3 ± 9.3	2.1 ± 8.2	−1.6 ± 10.2**	−3.0 ± 8.8	0.029
ΔBMI, kg/m^2	0.88 ± 2.8	0.65 ± 2.2	−0.41 ± 3.0	−0.79 ± 3.3	0.075
ΔBMI, %	3.62 ± 9.5	2.31 ± 8.4	−0.66 ± 9.5**	−5.95 ± 12.6	0.023
ΔWC, cm	5.1 ± 7.9	5.7 ± 6.3	1.4 ± 9.1	2.3 ± 1.3	0.101
ΔWC, %	5.8 ± 8.9	6.3 ± 6.9	2.0 ± 9.4	1.9 ± 0.7	0.142

BMI: body mass index; and WC: waist circumference. [a]Values expressed as mean ± SD. *p = 0.03 in relation to the non-COPD group. **p = 0.054 in relation to the non-COPD group.

prevalence of obesity in patients with mild obstruction, exceeding that seen in healthy individuals in the same age group. Stratified analysis of BMI by GOLD severity stage clearly shows that, because our sample consisted predominantly of individuals with GOLD stage I disease (62.5%), the overall mean BMI in the COPD group was high (29.1 ± 17.6 kg/m^2). In contrast, patients with GOLD stage II-III-IV disease experienced weight loss and a reduction in BMI over time, which is in line with the findings of a study that reported a prevalence rate of 18% for obesity in COPD, with 16% and 20% of obese individuals being classified as GOLD stage I and II, respectively, and only 6% being classified as GOLD stage IV.[32]

Several factors can contribute to weight loss in the course of COPD. In addition to the decline in caloric intake with aging,[33] a worsening of dyspnea during meals,[34] and a reduction in appetite,[35] there is increased energy expenditure due to changes in lung mechanics,[36] increased muscle energy cost,[37] and increased production of inflammatory mediators.[38] These factors support our findings of lower weight gain in patients with more severe forms of COPD.

One intriguing finding in our study was the stability of WC across all COPD stages, despite the weight reduction in individuals with moderate to severe disease. Patients with GOLD stage II COPD lost weight and had a reduction in BMI, but showed a 2% increase in WC. Temporal analysis of WC status revealed that individuals in both groups had difficulty reducing their WC: only slightly more than 10% of the individuals in the non-COPD group achieved a normal WC, whereas the proportion of reduction was even lower (4.5%) in the COPD group. This difficulty in losing abdominal fat despite weight loss may be linked to the increased risk of COPD patients for developing atherosclerotic diseases.[39]

We should point out some limitations of our study. Because of the population-based design of the PLATINO study, with all assessments being conducted in the participants' homes, some assessments that would be of interest could not be carried out. The diagnosis of COPD was based solely on the GOLD criteria, that is, a post-bronchodilator FEV_1/FVC ratio of < 070. Despite being widely used in epidemiological studies, this criterion is criticized because the use of a fixed cut-off point for the FEV_1/FVC ratio poses a risk of COPD being underdiagnosed in younger individuals and of its prevalence being overestimated in older individuals. However, this diagnostic criterion is widely accepted and is the one most widely used in epidemiological studies, allowing comparisons of the results of the PLATINO study with those of studies conducted in other countries and regions. The determination of nutritional status was based solely on BMI stratification, a method that cannot quantify body compartments and, therefore, may fail to identify patients with reduced lean body mass but no weight reduction. However, the literature points to BMI as the most practical way to diagnose obesity, and BMI is the most widely used method in epidemiological studies. Our study was not designed to determine the causes and consequences of the nutritional changes found, which would be of interest to measuring the impact of such findings on our population.

With this study, we can conclude that, in the follow-up phase of the PLATINO study, there was an increase in weight in both groups. Among the COPD patients, those with mild disease showed increases in weight and BMI, whereas those with more advanced stage disease showed reductions. These results show the importance of knowing the nutritional profile of COPD patients and preventing both weight loss and excess weight, given that underweight and overweight/obesity have a negative effect on prognosis.

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Multidisciplinary education with a focus on COPD in primary health care

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ABSTRACT

Objective: To evaluate the use of video lessons on the topic of COPD as a training tool for a multidisciplinary team working in the primary health care sector. **Methods:** This was a quasi-experimental study involving a multidisciplinary team working at a primary health care clinic. The level of knowledge about COPD was measured by applying a specific, 16-item questionnaire - before, immediately after, and three months after the video lessons. In a set of six structured video lessons, the training focused on the prevention, case-finding, treatment, and monitoring of cases of COPD. The data were analyzed with the Friedman test, the Kruskal-Wallis test, Tukey's post hoc test, Dunnett's test, and the Bonferroni test. **Results:** There was a significant difference between the periods before and immediately after the training in terms of the scores on 15 of the 16 items on the questionnaire regarding the level of knowledge about COPD. The median total score of the participants increased significantly, from 60 points before the training to 77 points immediately thereafter and 3 months thereafter ($p < 0.001$ for both). Before the training, 23 (63.9%) and 13 (36.1%) of the members of the multidisciplinary team presented strong and very strong levels of agreement, respectively, among the 16 questionnaire items. After the training, 100% of the individuals presented a very strong degree of agreement. **Conclusions:** Multidisciplinary education through video lessons increased the knowledge of COPD on the part of a primary health care team, and the knowledge acquired was retained for at least three months after the intervention.

Keywords: Instructional films and videos; Pulmonary disease, chronic obstructive; Inservice training; Primary health care; Education, medical.

INTRODUCTION

COPD is a highly prevalent condition in people over 40 years of age.[1] However, it is still underdiagnosed[2] in Brazil. One of the possible reasons for this is the low level of knowledge about COPD among primary health care professionals and patients.[3,4]

Reducing the inequalities that result from the very diverse and heterogeneous levels of knowledge and training among members of multidisciplinary primary health care teams is a challenge.[5-7] In order to overcome this challenge, one may use video lessons, an educational multimedia tool that includes images and narration of text in the format of short videos to be used in a safe and controlled learning environment.[8,9] However, to the best of our knowledge, this tool has not yet been used for teaching primary health care professionals about COPD. Therefore, the objective of the present study was to evaluate the use of video lessons as a tool for training a multidisciplinary primary health care team on COPD.

METHODS

This was a quasi-experimental study carried out at the *Centro de Saúde da Família Leste Universitário, Distrito Sanitário Campinas Centro*, located in the city of Goiânia, Brazil. The study was approved by the Research Ethics Committee of the Federal University of Goiás under protocol number 857.082/14.

Inclusion and exclusion criteria

Primary health care professionals were included in the study, and visually- and/or hearing-impaired professionals who would not be able to watch the video lessons and read the knowledge assessment instrument were excluded, as well as those who did not have time to participate in the sessions. We have chosen primary health care professionals for the territorial coverage of their work and convenience.

The instrument used to measure the level of knowledge of the multidisciplinary team was the *Questionário de Conhecimentos sobre a Doença Pulmonar Obstrutiva Crônica na Atenção Primária* (QAP-DPOC, Questionnaire about Knowledge on Chronic Obstructive Pulmonary Disease in Primary Health Care).[10] The QAP-DPOC was applied at three different time points: before, immediately after, and three months after the training sessions, with no interference by the evaluator. After the first application of the questionnaire, the training sessions began in a quiet room.

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Video lessons

The video lessons were filmed and edited by professionals of the *Núcleo de Telemedicina e Telessaúde* of the *Universidade Federal de Goiás* in Goiânia. A digital camcorder (Panasonic do Brasil, Manaus, Brazil), a tripod, and Adobe Connect software (Adobe System, San Jose, CA, USA) were used for recording; for editing, the Camtasia Studio 8 software (TechSmith, Okemos, MI, USA) was used on a personal computer. The video lessons were made available on DVD and, on the scheduled day, were shown at the *Centro de Saúde da Família* by means of an audiovisual device. A facilitator remained in the classroom to discuss any topics addressed by the lessons that might need clarification.

The telehealth platform of university was used to store the video lessons and make them available, should the professional wish to watch them again (http://www.tele.medicina.ufg.br/).

The training consisted of six video lessons taught by an instructor with experience in the subject matter, with the following themes (duration): management of patients with respiratory symptoms (21'30"); case-finding of patients at risk of COPD (16'00"); smoking cessation (20'23"); physical exercise for COPD patients (14'40"); referral, counter-referral, and clinical management of COPD exacerbations (14'45"); and guidance on the use of inhalers, vaccines, and oxygen therapy for COPD (32'13"). The video lessons addressed the topics of prevention, case-finding, treatment (pharmacological and nonpharmacological), and monitoring of COPD. It is important to note that the QAP-DPOC is not aimed at pulmonologists, but at multidisciplinary primary health care teams.[10]

Statistical analysis

The Shapiro-Wilk normality test was used to verify the distribution of the data. The continuous quantitative variables were presented as means, standard deviations, medians, and 95% CIs. The Friedman test was used to analyze the answers before, immediately after, and three months after the training provided. The Kruskal-Wallis test was used in order to compare the level of knowledge among the professionals. For greater accuracy in the detection of significant differences, Tukey's *post hoc* multiple comparisons test and Dunnett's test were used. The Bonferroni correction was used to prevent type I errors. For all situations, a significance level of 5% was used.

RESULTS

Thirty-eight primary health care professionals were considered eligible for the study. Two individuals did not complete the protocol and were excluded from the final analysis. Of the total of 36 participants, 30 (83.3%) were female. In the sample as a whole, 9 participants (25.0%) were community agents; 8 (22.2%) were nurses; 6 (16.7%) were nursing assistants; 6 (16.7%) were physicians; and 7 (19.4%) were dentists. As for the level of education of the participants, 11 (30.6%) had a high school diploma; 4 (11.1%) had some college education; 10 (27.8%) had an undergraduate degree; 1 (2.8%) had some graduate education; and 10 (27.8%) had a graduate degree. The age ranged from 24 to 75 years (mean = 40.2 ± 12.3 years). The average time as a member of a multidisciplinary team working in primary health care was 128.5 ± 118.5 months.

The professionals who checked the "agree" option before the training, checked the "fully agree" option immediately after the sessions for most of the questions (11 items; 68.8%; Table 1). Comparing the answers provided before and immediately after the training, there was an increase in the rate of correct answers to the 16-item questionnaire, which was maintained at the evaluation performed three months later ($p < 0.05$). Answers considered correct are shown in Table 1. A 75% agreement with the correct answer in a specific item of the questionnaire was considered "right". Item 7 presented significant differences in all comparisons (Table 2).

The questionnaire has a minimum score of 16 points, which indicates a low level of knowledge about COPD, and a maximum score of 80 (highest level of knowledge). The median score of the participants in the questionnaire increased from 60 before the training to 77 immediately thereafter and three months thereafter ($p < 0.001$ for both). The mean score also increased immediately after the training, and it was kept the same three months thereafter.

Before our intervention, there was greater score dispersion among the participants, whereas immediately after the training and three months thereafter, there were only one and four outliers below the median score, respectively, which did not influence the final result. After the intervention, the homogeneity of the results (level of knowledge) clearly increased (Figure 1).

Prior to the training, 23 (63.9%) and 13 (36.1%) of the members of the multidisciplinary team presented strong and very strong degrees of agreement in the 16 items of the questionnaire, respectively. After the training, 100% of the individuals presented a very strong degree of agreement.

We compared the level of knowledge among the different professionals of the primary health care team before the training. We found out that community agents and nursing technicians were the ones with the lowest levels of knowledge when compared with physicians ($p < 0.05$). After the training, there were no differences in the level of knowledge among the different professionals. Three months after the training, community agents presented a more significant reduction in their level of knowledge when compared with nurses ($p < 0.05$). The results are shown in Table 3.

Table 1. Absolute values and proportions of participants from a multidisciplinary primary health care team (N = 36) who have checked each response in the Questionnaire about Knowledge on Chronic Obstructive Pulmonary Disease in Primary Health Care at three different time points, means, standard deviations, medians, and 95% CIs of the scores in the general sample.

Response per item	Participants, n (%)					Scores	
	1 Strongly disagree	2 Disagree	3 Undecided	4 Agree	5 Strongly agree	Mean ± SD	Median (95% CI)
1) Being a smoker/former smoker is not a risk factor for COPD.							
1-A	22 (61.1)[a]	9 (25.0)	1 (2.8)	0 (0)	4 (11.1)	1.75 ± 1.27	1.00 (1.31-2.18)
1-B	30 (83.3)[a]	5 (13.9)	0 (0)	0 (0)	1 (2.8)	1.25 ± 0.73	1.00 (1.00-1.49)
1-C	30 (83.3)[a]	5 (13.9)	0 (0)	0 (0)	1 (2.8)	1.5 ± 0.73	1.00 (1.00-1.49)
2) The leading causes of COPD are cigarette smoking and wood stove smoke.							
2-A	1 (2.8)	3 (8.3)	1 (2.8)	21 (58.3)	10 (27.8)[a]	4.00 ± 0.95	4.00 (3.76-4.32)
2-B	0 (0)	0 (0)	0 (0)	5 (13.9)	31 (86.1)[a]	4.86 ± 0.35	5.00 (4.74-4.97)
2-C	0 (0)	0 (0)	0 (0)	3 (8.3)	33 (91.7)[a]	4.92 ± 0.28	5.00 (4.82-5.01)
3) Counseling for approximately 3 to 10 minutes can help patients quit smoking.							
3-A	5 (13.9)	7 (19.4)	6 (16.7)	14 (38.9)	4 (11.1)[a]	3.13 ± 1.26	3.50 (2.70-3.56)
3-B	2 (5.6)	0 (0)	0 (0)	3 (8.3)	31 (86.1)[a]	4.69 ± 0.95	5.00 (4.37-5.01)
3-C	1 (2.8)	0 (0)	3 (8.3)	6 (16.7)	25 (72.2)[a]	4.56 ± 0.87	5.00 (4.25-4.85)
4) Group counseling is not a primary health care action aimed at assisting patients undergoing a critical smoking withdrawal phase.							
4-A	16 (44.4)[a]	14 (38.9)	3 (8.3)	2 (5.6)	1 (2.8)	1.83 ± 1.00	2.00 (1.49-2.17)
4-B	32 (88.9)[a]	1 (2.8)	0 (0)	0 (0)	3 (8.3)	1.36 ± 1.12	1.00 (0.98-1.74)
4-C	31 (86.1)[a]	4 (11.1)	0 (0)	0 (0)	1 (2.8)	1.22 ± 0.72	1.00 (0.97-1.46)
5) Magazines and booklets are ways to educate COPD patients about their health care.							
5-A	0 (0)	0 (0)	3 (8.3)	20 (55.6)	13 (36.1)[a]	4.27 ± 0.61	4.00 (4.06-4.48)
5-B	0 (0)	0 (0)	0 (0)	2 (5.6)	34 (94.4)[a]	4.94 ± 0.23	5.00 (4.86-5.02)
5-C	0 (0)	0 (0)	0 (0)	5 (13.9)	31 (86.1)[a]	4.86 ± 0.35	5.00 (4.74-4.97)
6) COPD symptoms appear slowly and progressively.							
6-A	0 (0)	0 (0)	3 (8.3)	21 (58.3)	12 (33.3)[a]	4.25 ± 0.60	4.00 (4.04-4.45)
6-B	0 (0)	0 (0)	0 (0)	4 (11.1)	32 (88.9)[a]	4.88 ± 0.31	5.00 (4.78-4.99)
6-C	0 (0)	0 (0)	0 (0)	5 (13.9)	31 (86.1)[a]	4.86 ± 0.35	5.00 (4.74-4.97)
7) Frequent cough is a symptom of COPD.							
7-A	1 (2.8)	6 (16.7)	12 (33.3)	14 (38.9)	3 (8.3)[a]	3.33 ± 0.95	3.00 (3.01-3.65)
7-B	0 (0)	0 (0)	0 (0)	3 (8.3)	33 (91.7)[a]	4.91 ± 0.28	5.00 (4.82-5.01)
7-C	0 (0)	1 (2.8)	1 (2.8)	9 (25.0)	25 (69.4)[a]	4.61 ± 0.68	5.00 (4.37-4.84)
8) Influenza and pneumonia vaccines do not reduce the number of COPD exacerbations.							
8-A	7 (19.4)[a]	14 (38.9)	6 (16.7)	7 (19.4)	2 (5.6)	2.52 ± 1.18	2.00 (2.12-2.92)
8-B	26 (72.2)[a]	6 (16.7)	0 (0)	1 (2.8)	3 (8.3)	1.58 ± 1.20	1.00 (1.17-1.99)
8-C	28 (77.8)[a]	3 (8.3)	1 (2.8)	2 (5.6)	2 (5.6)	1.53 ± 1.15	1.00 (1.13-1.91)
9) The use of oxygen in COPD patients will cause dependence.							
9-A	6 (16.7)[a]	17 (47.2)	8 (22.2)	5 (13.9)	0 (0)	2.33 ± 0.92	2.00 (2.02-2.64)
9-B	29 (80.6)[a]	6 (16.6)	0 (0)	0 (0)	1 (2.8)	1.27 ± 0.74	1.00 (1.02-1.52)
9-C	27 (75.0)[a]	8 (22.2)	0 (0)	1 (2.8)	0 (0)	1.31 ± 0.62	1.00 (1.09-1.51)
10) Practicing physical exercise can improve the autonomy and physical/social performance of COPD patients.							
10-A	0 (0)	1 (2.8)	0 (0)	22 (61.1)	13 (36.1)[a]	4.30 ± 0.62	4.00 (4.09-4.51)
10-B	0 (0)	0 (0)	0 (0)	2 (5.6)	34 (94.4)[a]	4.94 ± 0.23	5.00 (4.86-5.02)
10-C	0 (0)	0 (0)	0 (0)	4 (11.1)	32 (88.9)[a]	4.89 ± 0.31	5.00 (4.78-4.99)
11) As part of COPD treatment, it is important to talk about the myths and prejudices against the use of inhalers, oxygen therapy, and physical exercise.							
11-A	0 (0)	0 (0)	4 (11.1)	23 (63.9)	9 (25.0)[a]	4.13 ± 0.59	4.00 (3.93-4.33)
11-B	0 (0)	0 (0)	0 (0)	5 (13.9)	31 (86.1)[a]	4.86 ± 0.35	5.00 (4.74-4.97)
11-C	0 (0)	0 (0)	0 (0)	7 (19.4)	29 (80.6)[a]	4.81 ± 0.40	5.00 (4.66-4.94)

A: before the training; B: immediately after the training; and C: three months after the training. [a]Indicates the correct answer.

Table 1. Continued...

Response per item	Participants, n (%)					Scores	
	1 Strongly disagree	2 Disagree	3 Undecided	4 Agree	5 Strongly agree	Mean ± SD	Median (95% CI)
12) The right sequence for using inhaled medications is: 1) exhale normally, 2) place the mouthpiece in your mouth, 3) inhale deeply, 4) close your mouth and hold the air in your lungs for approximately ten seconds.							
12-A	1 (2.8)	2 (5.6)	16 (44.4)	8 (22.2)	9 (25.0)[a]	3.61 ± 1.02	3.00 (3.26-3.95)
12-B	0 (0)	0 (0)	0 (0)	5 (13.9)	31 (86.1)[a]	4.86 ± 0.35	5.00 (4.74-4.97)
12-C	0 (0)	0 (0)	3 (8.3)	3 (8.3)	30 (83.3)[a]	4.75 ± 0.60	5.00 (4.54-4.95)
13) The treatment of COPD includes: pharmacological and nonpharmacological therapy, education, and guidance on a healthy life style.							
13-A	0 (0)	1 (2.8)	1 (2.8)	22 (61.1)	12 (33.3)[a]	4.25 ± 0.64	4.00 (4.03-4.46)
13-B	0 (0)	0 (0)	0 (0)	3 (8.3)	33 (91.7)[a]	4.91 ± 0.28	5.00 (4.82-5.01)
13-C	0 (0)	0 (0)	0 (0)	4 (11.1)	32 (88.9)[a]	4.89 ± 0.31	5.00 (4.78-4.99)
14) The term "counter-referral" means: COPD patients referred to the primary health care center by a secondary or tertiary health care center, along with information on their diagnosis and treatment.							
14-A	0 (0)	0 (0)	15 (41.6)	10 (27.8)	11 (30.6)[a]	3.88 ± 0.85	4.00 (3.59-4.17)
14-B	0 (0)	1 (2.8)	1 (2.8)	1 (2.8)	33 (91.6)[a]	4.83 ± 0.60	5.00 (4.62-5.03)
14-C	0 (0)	0 (0)	0 (0)	3 (8.3)	33 (91.7)[a]	4.92 ± 0.28	5.00 (4.82-5.01)
15) When the health care team provides guidance on physical exercise to COPD patients, it is important to provide them with a scale to manage their shortness of breath.							
15-A	0 (0)	1 (2.8)	13 (36.1)	17 (47.2)	5 (13.9)[a]	3.72 ± 0.73	4.00 (3.47-3.97)
15-B	0 (0)	0 (0)	0 (0)	7 (19.4)	29 (80.6)[a]	4.80 ± 0.40	5.00 (4.55-4.94)
15-C	0 (0)	0 (0)	1 (2.8)	7 (19.4)	28 (77.8)[a]	4.75 ± 0.50	5.00 (4.58-4.91)
16) All patients who are diagnosed with COPD should be referred to a pulmonologist.							
16-A	1 (2.8)	5 (13.9)[a]	3 (8.3)	19 (52.8)	8 (22.2)	3.77 ± 1.04	4.00 (3.42-4.13)
16-B	7 (19.5)	26 (72.2)[a]	0 (0)	2 (5.5)	1 (2.8)	2.00 ± 0.82	2.00 (1.71-2.28)
16-C	3 (8.3)	26 (72.2)[a]	2 (5.6)	2 (5.6)	3 (8.3)	2.33 ± 1.01	2.00 (1.99-2.67)

A: before the training; B: immediately after the training; and C: three months after the training. [a]Indicates the correct answer.

DISCUSSION

Our findings show that the level of knowledge of the multidisciplinary primary health care team immediately after the training on COPD was higher than before the training, and that this knowledge was retained up to three months afterwards. The findings also indicate that the members of the team who held lower- and middle-level positions presented a greater knowledge deficit.

We found no studies regarding the use of video lessons to monitor the changes in the levels of knowledge among primary health care professionals in Brazil. Therefore, this study helps to determine the level of knowledge about COPD of primary health care professionals and to show how heterogeneous it is.

Two positive and pioneering aspects of the study were that it used video lessons as an educational tool for a multidisciplinary team whose members had different levels of education and training on COPD, and that it used a questionnaire that was specifically designed and validated to measure the level of knowledge of primary health care professionals on COPD. The questionnaire on COPD for primary health care professionals designed and validated for our study followed national and international recommendations.[11,12]

Our study reflects the level of knowledge of the population investigated so that it can be used as a baseline measure for future interventions in public health, making it possible to compare the levels of knowledge on COPD of multidisciplinary primary health care teams in different regions. The idea is to train different primary health care professionals without any sort of stratification, as this would prevent the training of a multidisciplinary team.

Two studies[8,9] used video lessons to investigate the use of different teaching methods with medical students and specialist physicians. Those studies consider video lessons a new pedagogical approach that can be used in order to improve this population's academic skills and self-confidence in providing care.

Fifteen of the 16 items of the QAP-DPOC showed significant differences between the moments before and immediately after the training; and 14 items did not show significant differences between immediately after the training and three months thereafter, the only exceptions were items 7 and 13. In item 7, immediately after the training, there was a shift from the option "fully agree" to the option "agree", which represented a significant difference; however, this was a small change and we do not believe it is clinically relevant.

Table 2. Results of the Friedman test comparing the responses to each item of the Questionnaire about Knowledge on Chronic Obstructive Pulmonary Disease in Primary Health Care.

Item	A	B	C	p[a]	p[b]	p[c]
	Score, mean ± SD					
1	1.75 ± 1.27	1.25 ± 0.73	1.25 ± 0.73	0.03	0.06	0.85
2	4.00 ± 0.96	4.86 ± 0.35	4.92 ± 0.28	< 0.001	< 0.001	0.48
3	3.14 ± 1.27	4.69 ± 0.95	4.56 ± 0.88	< 0.001	< 0.001	0.32
4	1.83 ± 1.00	1.36 ± 1.13	1.22 ± 0.72	< 0.001	< 0.001	0.48
5	4.28 ± 0.61	4.94 ± 0.23	4.86 ± 0.35	< 0.001	< 0.001	0.26
6	4.25 ± 0.60	4.89 ± 0.32	4.86 ± 0.35	< 0.001	< 0.001	0.71
7	3.33 ± 0.96	4.92 ± 0.28	4.61 ± 0.69	< 0.001	< 0.001	0.01
8	2.53 ± 1.18	1.58 ± 1.20	1.53 ± 1.16	< 0.001	< 0.001	0.59
9	2.33 ± 0.93	1.28 ± 0.74	1.31 ± 0.62	< 0.001	< 0.001	0.33
10	4.31 ± 0.62	4.94 ± 0.23	4.89 ± 0.32	< 0.001	< 0.001	0.32
11	4.14 ± 0.59	4.86 ± 0.35	4.81 ± 0.40	< 0.001	< 0.001	0.48
12	3.61 ± 1.02	4.86 ± 0.35	4.75 ± 0.60	< 0.001	< 0.001	0.33
13	4.25 ± 0.65	4.92 ± 0.28	4.89 ± 0.32	0.71	< 0.001	< 0.001
14	3.89 ± 0.85	4.83 ± 0.61	4.92 ± 0.28	< 0.001	< 0.001	0.48
15	3.72 ± 0.74	4.81 ± 0.40	4.75 ± 0.50	< 0.001	< 0.001	0.59
16	3.78 ± 1.05	2.00 ± 0.83	2.33 ± 1.01	< 0.001	< 0.001	0.56

A: before the training; B: immediately after the training; and C: three months after the training. [a]A vs. B. [b]A vs. C. [c]B vs. C.

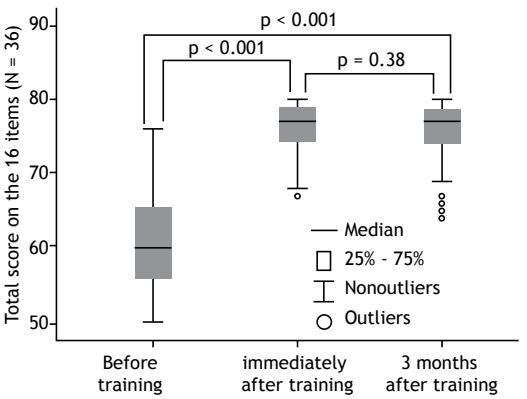

Figure 1. Box plot of the comparison of the total score on the 16-item Questionnaire about Knowledge on Chronic Obstructive Pulmonary Disease in Primary Health Care at the different time points (before, immediately after, and three months after the professional training with video lessons).

A study[13] evaluated the knowledge of people at risk of COPD and stated that 70% of smokers believed that the knowledge of primary health care physicians represented more than just a source of health advice when compared with advice given by family and friends, emphasizing the importance of the knowledge and conduct of primary health care professionals to educate patients and change their behavior.

It is particularly challenging to conduct studies on the COPD expertise of multidisciplinary primary health care teams because team members present very diverse levels of knowledge. The results of a study[3] and our findings indicate the need to train the multidisciplinary primary health care team in order to promote better community education action plans. This fact could, in an optimistic view, contribute to reducing the prevalence of smoking among young adults.[14]

A study[15] carried out in the Middle East and North Africa asked 1,392 patients to complete a questionnaire about their knowledge on COPD and satisfaction with the treatment they had been given. Overall, 58.6% of the patients stated they were properly informed about their respiratory condition; 66% reported having received information about COPD from their physician; 11% from television; 6% from the Internet; and below 1% from other health care professionals.[15] In that study, 47.5% of the individuals interviewed considered the physician important in managing respiratory symptoms and believed that the knowledge of physicians and other health care professionals created a closer and stronger professional-patient relationship. However, it is important to note that, in our field, plenty of useful primary health care information is provided by nonmedical professionals.[3] Therefore, there is no doubt that primary health care users have a knowledge gap about COPD and that this gap should be filled. Primary health care users could certainly benefit from the expansion of knowledge of their multidisciplinary team.

We clearly noticed that, after the intervention, there was an increase in the number of responses considered correct in the questionnaire. These results indicate that the knowledge that was demystified and imparted to primary health care professionals during the training on COPD can increase the transfer of educational information about the condition to the patients seen by these professionals. The authors of the aforementioned study[15] believe that the rate of COPD-related information transfer by other health care professionals (< 1%) should be overcome.

The frequency of responses considered correct three months after the training was superior to 50% for all

Table 3. Results of the test of multiple comparisons of the scores obtained on the Questionnaire about Knowledge on Chronic Obstructive Pulmonary Disease in Primary Health Care by type of health care professional at each of the three time points.

Time point	Primary health care professionals					
	Community agent	Dentist	Nurse	Physician	Nursing assistant	p*
	Total score, mean ± SD					
A	57.00 ± 5.17†	61.86 ± 5.52	61.75 ± 4.98	67.17 ± 6.49††	57.17 ± 4.17	0.02
B	74.67 ± 3.91	77.57 ± 2.07	77.63 ± 2.00	77.50 ± 2.43	72.67 ± 4.89	0.10
C	72.11 ± 5.67¶	75.71 ± 3.45	77.88 ± 1.36	77.00 ± 4.05	73.67 ± 3.93	0.03

A: before the training; B: immediately after the training; and C: three months after the training. *The Kruskal-Wallis test, followed by Tukey's post hoc test and Dunnett's test. †$p < 0.05$ between community agents and physicians. ††$p < 0.05$ between nursing assistants and physicians. ¶$p < 0.05$ between community agents and nurses.

items, which shows that the knowledge was retained during this period of time. These results corroborate those of another study[16] which obtained 54.7% agreement on the COPD-related knowledge of patients and health care professionals after an eight-week educational program; a group of authors[17] evaluated the level of knowledge of nurses on heart failure and found 70% agreement, however, they did not specify the elapsed time interval; and a study carried out in Brazil[6] on oral health knowledge in primary health care indicated a knowledge retention rate of 86.2% three months after the training provided. In our study population, the results support the retention of the knowledge acquired up to three months after the intervention, which indicates the importance of retaining knowledge about the condition through continuous education programs for multidisciplinary primary health care teams.

Primary health care usually focuses on meeting spontaneous demand, whereas preventive actions are capable of anticipating risks and even diagnosing diseases earlier. In this sense, guidance on prevention could provide users with a more integral care, which is a guiding principle of the Brazilian Unified Health System and in various other countries.[18]

Different training strategies have been implemented in an attempt to address the complexity of multidisciplinary primary health care teams.[19] We chose to use video lessons because it is a teaching tool that can be used in a distance learning setting, creating teaching/learning opportunities for health care professionals.[8,20]

The effect of the knowledge evolution of our study population can be identified by the increased rate of responses considered correct for each item after the training and by the change in the degree of agreement on the items investigated (from strong to very strong agreement). This effect was anticipated in a study[8] which considered video lessons a new and challenging resource capable of decentralizing knowledge and promoting the improvement of health competencies among individuals with different levels of knowledge, such as those of our study population. Thus, our study fills two gaps: the lack of studies investigating knowledge about COPD among primary health care professionals and the possibility of training these professionals on COPD using a reproducible method.

The use of video lessons shortens geographic distances and promotes sustained knowledge in different communities. According to a group of authors,[21] the limited knowledge on COPD identified in interviews with health care professionals in South Africa, Japan, and Hong Kong indicates the need to improve knowledge, which can be accomplished through the use of video lessons.

Video-based continuing education is still an underused strategy for continuing training in health care in Brazil and it has the potential to expand multidisciplinary actions, integrating them into health care services. The literature[22] indicates a need to reflect upon and reformulate andragogical practices, as well as to focus on contents that have practical everyday applications for professionals. Video lessons are a teaching tool that meets such andragogical needs.[22]

The increase in the median score of participants seen immediately after our intervention and maintained three months thereafter shows the effectiveness of video-based training. Although the work of primary health care teams is quite complex, mainly educational in nature, their professional training is usually poor.[6] Therefore, the purpose of our intervention was to encourage interdisciplinarity and inform team members about COPD, one of the noncommunicable chronic diseases with high rates of morbidity and mortality worldwide, through the use of video lessons, an effective knowledge multiplier and driver of change.[6,23-25]

A multidisciplinary approach to education enables the patient-professional bond to be established and gives patients co-responsibility for their care, as they take on an active role in their health-related decision-making process.[26] When the team members are confident about their knowledge, the guidance provided and the communication actions implemented by them are enhanced and can minimize the conflicts between the community and the health care services.[19]

The present study showed us that video-based training can fill in the knowledge gaps of primary health care professionals. Our experience can also be used as a basis for planning future interventions.

The recommendation is that all members of the multidisciplinary primary health care team be trained.[19]

However, our study has limitations, such as the small number among the different professionals in the primary health care team and the absence of a control group. The small number of different professionals was due to the fact that we wanted to recruit a group of professionals from the same primary health care institution. As for the absence of a control group, we believe that our findings were due to the training provided, since the questionnaire was not made available to the participants and they had free access to the video lessons throughout the study period so that they could clarify any possible doubts.

The idea of using video lessons with different categories of health care professionals is justified by the characteristics of primary health care teams. Although physicians are clinically responsible for COPD patients, their goals would not be achieved without the support of the multidisciplinary team. In this context, we must recognize that all primary health care professionals benefit from professional training.[19]

Regarding the clinical benefit of the present study, we can highlight that training with video lessons can help the multidisciplinary primary health care team to identify possible COPD patients. This teaching model gives the team confidence to recognize COPD risk factors and symptoms, as well as the different types of pharmacological and nonpharmacological treatments available and the need for patient monitoring. Patients greatly benefit since they have access to the right information provided by the primary health care team.

Therefore, we can conclude that video-based training promoted the acquisition of knowledge about COPD by the members of a multidisciplinary primary health care team, who retained the knowledge for at least three months after the intervention. In future studies, it would be important to evaluate for how long the information is retained, which will determine whether or not the training should be repeated periodically.

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Trends in morbidity and mortality from COPD in Brazil, 2000 to 2016

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ABSTRACT

Objective: To examine the trends in overall COPD mortality, as well as trends in in-hospital morbidity and mortality due to COPD, in Brazil, and to validate predictive models. **Methods:** This was a population-based study with a time-series analysis of cause-specific morbidity and mortality data for individuals ≥ 40 years of age, obtained from national health information systems for the 2000-2016 period. Morbidity and mortality rates, stratified by gender and age group, were calculated for the same period. We used regression analyses to examine the temporal trends and double exponential smoothing in our analysis of the predictive models for 2017. **Results:** Over the study period, COPD mortality rates trended downward in Brazil. For both genders, there was a downward trend in the southern, southeastern, and central-western regions. In-hospital morbidity rates declined in all regions, more so in the south and southeast. There were significant changes in the number of hospitalizations, length of hospital stay, and hospital expenses. The predictive models for 2017 showed error rates below 9% and were therefore validated. **Conclusions:** In Brazil, COPD age-adjusted mortality rates have declined in regions with higher socioeconomic indices, where there has been an even sharper decrease in all in-hospital morbidity and mortality variables. In addition to factors such as better treatment adherence and reduced smoking rates, socioeconomic factors appear to be involved in controlling COPD morbidity and mortality. The predictive models estimated here might also facilitate decision making and the planning of health policies aimed at treating COPD.

Keywords: Pulmonary disease, chronic obstructive/mortality; Pulmonary disease, chronic obstructive/epidemiology; Socioeconomic factors.

INTRODUCTION

The prevalence of COPD has increased worldwide and is now considered the third leading cause of death.[1,2] In Brazil, the overall COPD mortality rate showed a trend toward an increase between 1998 and 2004, and a decline from 2004 to 2009. In the 1998-2004 period, that rate increased in all regions of the country, declining thereafter only in the southern and southeastern regions.[3] The pattern for the age-adjusted COPD mortality rate was similar to that observed for the overall rate.[4]

Morbidity related to the natural history of COPD, especially infectious exacerbations and hospitalizations, is also considered relevant, as are smoking-related diseases, which are responsible for considerable morbidity and mortality, especially in the more severe forms of COPD.[5-9] Those factors contribute to increased absenteeism at work and early retirement, thereby promoting an increase in the direct and indirect costs associated with the disease.[10-12]

In Brazil, the history of public health policies to control smoking and prevent COPD began approximately three decades ago, culminating in a reduction in the prevalence of smoking in the country.[13,14] However, measures aimed at treating COPD are more recent developments, involving the distribution of inhaled medications provided at no cost by public health facilities, thereby benefiting patients undergoing specialist care. Adherence to treatment is one of the main objectives of the follow-up of patients with COPD. Some authors have shown that the rates of treatment abandonment are higher among women and among individuals who visit a specialist less frequently.[15] Other authors have reported that higher treatment adherence rates are associated with optimal socioeconomic conditions.[16]

Because Brazil is a country of continental dimensions, comprising macro-regions with different socioeconomic characteristics, a time-series analysis of COPD-related morbidity and mortality would aid in the evaluation of prevention strategies and current treatment. Therefore, the aims of this study were to examine the temporal trends in COPD mortality rates in the various macro-regions and to evaluate the temporal trends in in-hospital morbidity and mortality related to COPD, as well as to estimate and validate predictive models for the rates and variables considered.

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METHODS

Study design and setting

This was an ecological, population-based, analytical exploratory study with a time-series analysis of data related to the morbidity and mortality associated with COPD in Brazil. The dataset was limited to individuals ≥ 40 years of age and to the period of January of 2000 to December of 2016.

Public-use data were obtained from the information systems of the Brazilian National Ministry of Health and the Information Technology Department of the Brazilian Unified Health Care System,[17] including death certificates (sorted by place of residence), the number of hospitalizations, and length of hospital stays, all identified as related to COPD as defined in the International Classification of Diseases, 10th revision (ICD-10). Data for the resident population, based on the two most recent demographic censuses (2000 and 2010) and on population estimates for the non-census years (2001-2009 and 2011-2017), by age group, are publicly accessible and were obtained from the Brazilian Institute of Geography and Statistics.[18]

Study participants

The study population consisted of individuals ≥ 40 years of age residing in Brazil during the study period.

Statistical analysis

In this study, COPD was defined as a condition meeting the criteria of ICD-10 codes J41-J44. The ICD-10 codes J40 and J47 were not included, the first because it did not specify whether the disease was acute or chronic and the second because it referred to bronchiectasis, a term that, in Brazil, is closely associated with the sequelae of pulmonary tuberculosis.

The variables used in the time-series analysis were selected on the basis of a preliminary analysis of the data obtained for the number of deaths, the age-adjusted mortality rate by place of residence, the number of hospitalizations, the length of hospital stays, and hospital expenses.[19,20] In addition, these outcomes were stratified by geographic macro-region (north, northeast, central-west, south, and southeast), by gender, and by age group (40-49, 50-59, 60-69, 70-79, and ≥ 80 years).

For each macro-region, the annual mortality rate per 100,000 population was calculated on the basis of the number of deaths from COPD/resident population, stratified by gender and age group. To determine the change in mortality rates from 2000 to 2016, the 2016:2000 ratios for each macro-region were then calculated, also by gender and age range.

The annual in-hospital COPD age-adjusted mortality rates were determined by calculating the ratio between the number of deaths and the number of persons by place of residence during the year in question, multiplied by 100,000 and then multiplied by the percentage distribution of the standardized population. The data regarding the population adopted for standardization was obtained from the 2010 census.[18-20]

The annual number of hospitalizations was defined as the total number of hospitalizations due to COPD recorded in a given year. The length of hospital stay referred to the total number of days of hospitalization. Finally, the total hospital expense was defined as the cost of hospitalization during the period. The defined underlying causes of death were then recorded for the period from January of 2000 to December of 2016, and the COPD mortality rates were calculated, by place of residence, for the years 2000 and 2016, after which the 2016:2000 ratio was calculated by gender, age group, and macro-region.

To analyze the temporal trend during the studied period, we identified the regression equation that best described the relationship for each outcome, by gender and macro-region. For the hospital outcomes (age-adjusted in-hospital mortality rate, number of hospitalizations, length of hospital stay, and hospital expenses), we calculated the average annual percentage change (APC) in the indicators for the entire study period and the APC estimated for each time segment detected, with the respective 95% confidence intervals, from the regression model, using the Joinpoint Regression Program, version 4.6.0.0 (National Cancer Institute, Bethesda, MD, USA). In the APC analysis, inflection points were used in order to test whether a segmented line is significantly better than a straight line and whether a line with many segments is better than a line with fewer segments. To find the number of significant joinpoints, we used a permutation test.[21]

Finally, we performed an analysis involving double exponential smoothing, with the aim of estimating the age-adjusted in-hospital mortality rate, as well as the number and duration of hospitalizations due to COPD for the year 2017, using Minitab Statistical Software, version 18.0 (Minitab Inc., State College, PA, USA). The models were chosen by optimizing the parameters and measures of accuracy, including the mean absolute percentage error, the mean absolute deviation, and the mean squared deviation. The model selected was the one that minimized those three combined measurements. The final model was validated by calculating the percentage error between the observed and estimated values for the year 2017, with a significance level of 5%.

Ethical aspects

The data used in this study were from a secondary, anonymized source, available for public use and providing no information regarding individual identification. The study was approved by the local research ethics committee (CAAE no. 0055691.18.1.0000.5200; Protocol no. 2.954.260).

RESULTS

In Brazil, COPD was the fourth leading cause of death from 2000 to 2006, the fifth leading cause

of death from 2007 to 2014, and the fourth leading cause of death again from 2015 to 2016 (Figure 1). We observed variations in the 2016:2000 ratio for the COPD mortality rate among the macro-regions of the country. In the northern, northeastern, and central-west regions, the ratio was greater than 1.00 for both genders and in most age groups (Figures 2A, 2B, and 2C), whereas it was less than 1.00 for both genders and in all age groups in the southern and southeastern regions (Figures 2D and 2E). In the country as a whole, the 2016:2000 ratio for the COPD mortality rate was lower than 1.00 in both genders and in all of the age groups studied, indicating a downward temporal trend (Figure 2F). Figures 2J, 2K, and 2L show that there was an exponential increase in the COPD mortality rate in parallel with advancing age, with a similar presentation in the years 2000 and 2016, regardless of gender or macro-region.

In Brazil as a whole, there was a significant downward trend in the COPD mortality rate for both genders (Table 1). In the southern, southeastern, and central-western regions, there was a downward trend for both genders, whereas there was an upward trend in the other macro-regions. The number of hospitalizations and the length of hospital stays demonstrated a downward trend across Brazil and in all macro-regions, with a sharper reduction in the south and southeast (Table 1).

The joinpoint analysis for the in-hospital COPD mortality rate demonstrated a significant negative average APC for both genders (Table 2). The number of hospitalizations due to COPD and the length of hospital stay presented a negative, significant average APC for both genders, with a slight reduction in the APC for females from 2009 onward (Table 2). Hospital expenses presented a negative average APC for both genders, and the difference was significant for males. Until 2003, the APC was negative and significant for both genders, thereafter becoming positive only for females.

The predictive model estimates for in-hospital mortality rates, number of hospitalizations, and length of hospital stay are presented in Figure 3. All of the models presented mean absolute percentage errors of less than 7%. The values observed for the year 2017 were contained in the intervals with a 95% confidence interval and presented a percentage error of less than 9%, thereby validating the predictive models (Table 3).

DISCUSSION

We highlight two main findings of the present study. First, we observed a downward temporal trend in the COPD mortality rates in the macro-regions with higher socioeconomic indices.[22,23] Second, we observed a downward temporal trend in the in-hospital morbidity outcomes (number of hospitalizations, length of hospital stay, and hospital expenses) and mortality indicators in all regions, with a far more pronounced decrease in the regions exhibiting more favorable socioeconomic conditions.

In Brazil, the COPD age-adjusted mortality rate presented a significant decrease in both genders. This is similar to one study[1] that suggested that the decline in COPD mortality rates observed in certain countries is related to an increase in the gross income per capita in those countries. Within this context, our findings show that the COPD age-adjusted mortality rate presented different patterns in the southern, southeastern, and central-western regions of the country, where there were decreases for both genders, whereas there were increases in other regions. According to Brazilian Institute of Geography and Statistics data, the southern, southeastern and central-western regions have the lowest proportions of people with low incomes, the least social inequality, the lowest illiteracy rates in individuals ≥ 40 years of age, and the greatest proportional participation in the gross domestic product, in comparison with the

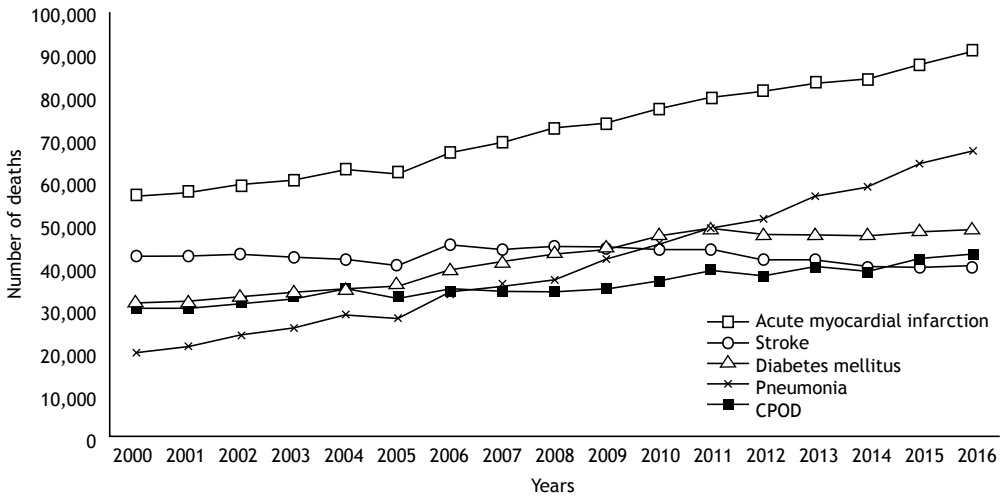

Figure 1. Trends of the underlying causes of death, according to the International Classification of Diseases, 10th revision, in Brazil, 2000-2016.

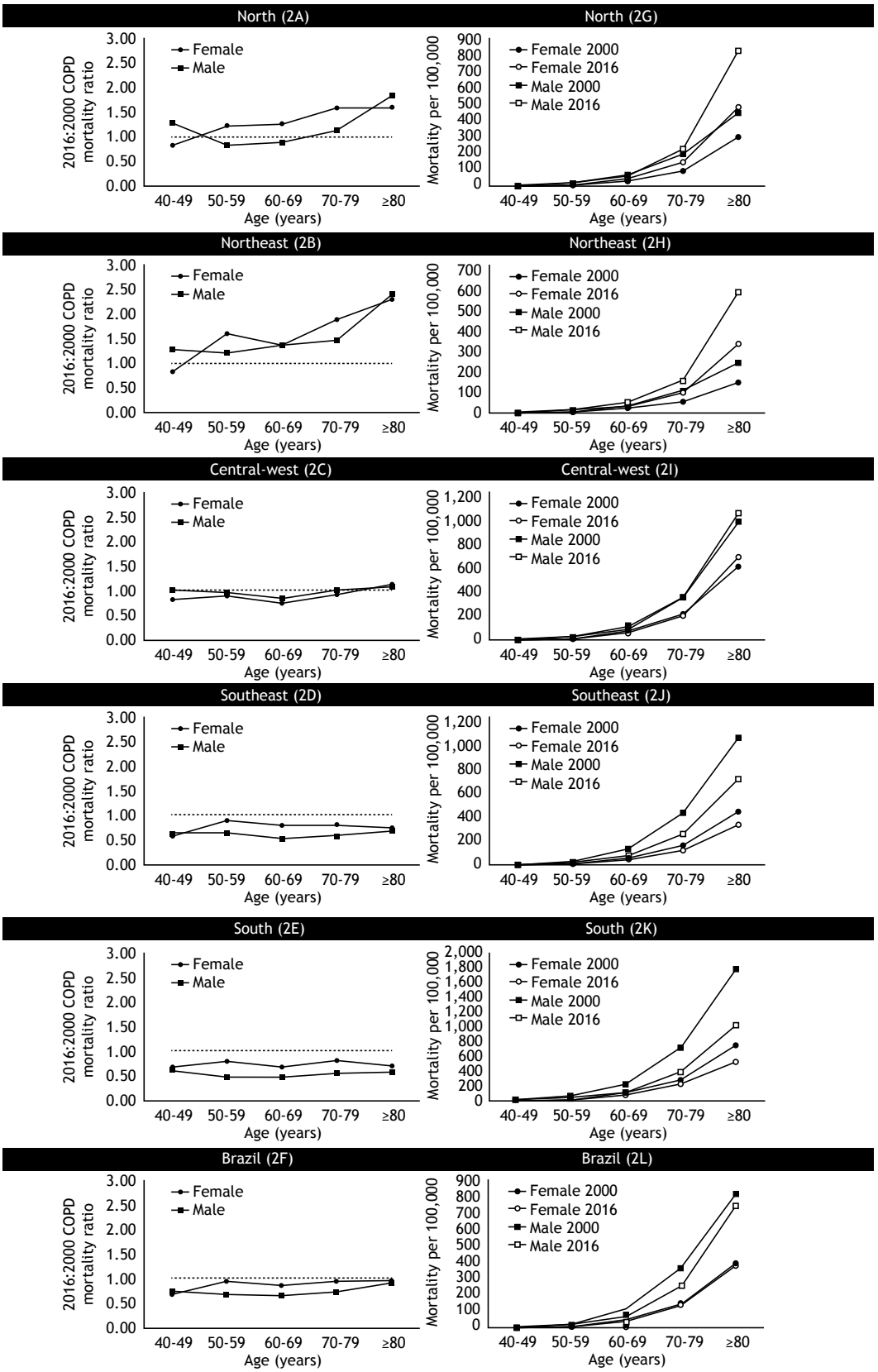

Figure 2. 2016:2000 COPD mortality ratios (A-F) and COPD mortality rates for the years 2000 and 2016 (G-L), by region, gender, and age group in Brazil, 2000-2016.

Table 1. Regression analysis for the age-adjusted mortality rate per 100,000 population, number of hospitalizations, and length of hospital stay, by gender and by region, among individuals with COPD in Brazil, 2000-2016.

Variable	Females		Males	
	β	R^2	β	R^2
Age-adjusted mortality rates				
Brazil	−0.2*	85.8	−0.4*	91.3
North	0.0	0.0	−0.1	16.7
Northeast	0.0	1.3	0.0	2.6
Southeast	−0.2*	86.5	−0.5*	91.4
South	−0.4*	85.3	−1.3*	92.2
Central-west	−0.3*	88.8	−0.4*	79.6
Hospitalizations				
Brazil	−4,057.7*	92.2	−5,352.9*	95.4
North	−122.5*	87.5	−155.4*	91.3
Northeast	−516.5*	81.8	−569.6*	89.9
Southeast	−1,162.8*	87.5	−1,594.5*	93.1
South	−1,839.9*	92.5	−2,505.7*	95.1
Central-west	−416.0*	95.2	−527.8*	94.6
Length of hospital stay, days				
Brazil	−18,603.6*	83.1	−29,801.0*	93.7
North	−545.5*	79.3	−710.7*	81.7
Northeast	−1,032.1	18.7	−2,708.6*	79.9
Southeast	−5,666.9*	74.3	−9,513.5*	92.0
South	−9,932.7*	89.6	−14,640.5*	93.4
Central-west	−1,426.4*	48.9	−2,227.7*	86.0

β: beta coefficient; and R^2: coefficient of determination. *p < 0.05.

Table 2. Joinpoint regression, standardized by age and gender, for in-hospital mortality rate, number of hospitalizations, length of hospital stay, and hospital expenses for COPD in Brazil, 2000-2016.

	Average APC	95% CI	Trend 1			Trend 2		
			Years	APC	95% CI	Years	APC	95% CI
In-hospital mortality								
Male	−5.6	(−6.3 to −4.8)	2000-2016	−5.6	(−6.3 to −4.8)			
Female	−4.2	(−5.1 to −3.3)	2000-2016	−4.2	(−5.1 to −3.3)			
Hospitalizations								
Male	−6.2	(−6.8 to −5.7)	2000-2016	−6.2	(−6.8 to −5.7)			
Female	−5.4	(−6.3 to −4.5)	2000-2009	−7.1	(−8.3 to −6.0)	2009-2016	−3.2	(−4.9 to −1.4)
Length of hospital stay, days								
Male	−5.7	(−6.3 to −5.0)	2000-2016	−5.7	(−6.3 to −5.0)			
Female	−4.1	(−5.2 to −3.0)	2000-2009	−6.8	(−8.2 to −5.4)	2009-2016	−0.5	(−2.7 to 1.7)
Hospital expenses								
Male	−1.3	(−2.4 to −0.2)	2000-2003	−7.3	(−12.8 to −1.4)	2003-2016	0.1	(−0.5 to 0.8)
Female	−0.6	(−1.9 to 0.7)	2000-2003	−9.8	(−16.1 to −3.1)	2003-2016	1.6	(0.9 to 2.4)

APC: annual percentage change.

other macro-regions.[23-25] Although we observed an increase in COPD mortality rates in the north and northeast regions between 2000 and 2016, an annual telephone survey showed a significant reduction in the proportions of smokers in all regions of the country from 2006 to 2014.[26]

Corroborating our findings of a decline in COPD age-adjusted mortality rates in the regions with higher socioeconomic indices, a hospital-based study conducted in Denmark reported higher adherence and lower mortality rates among individuals with a higher income, although it should be borne in mind

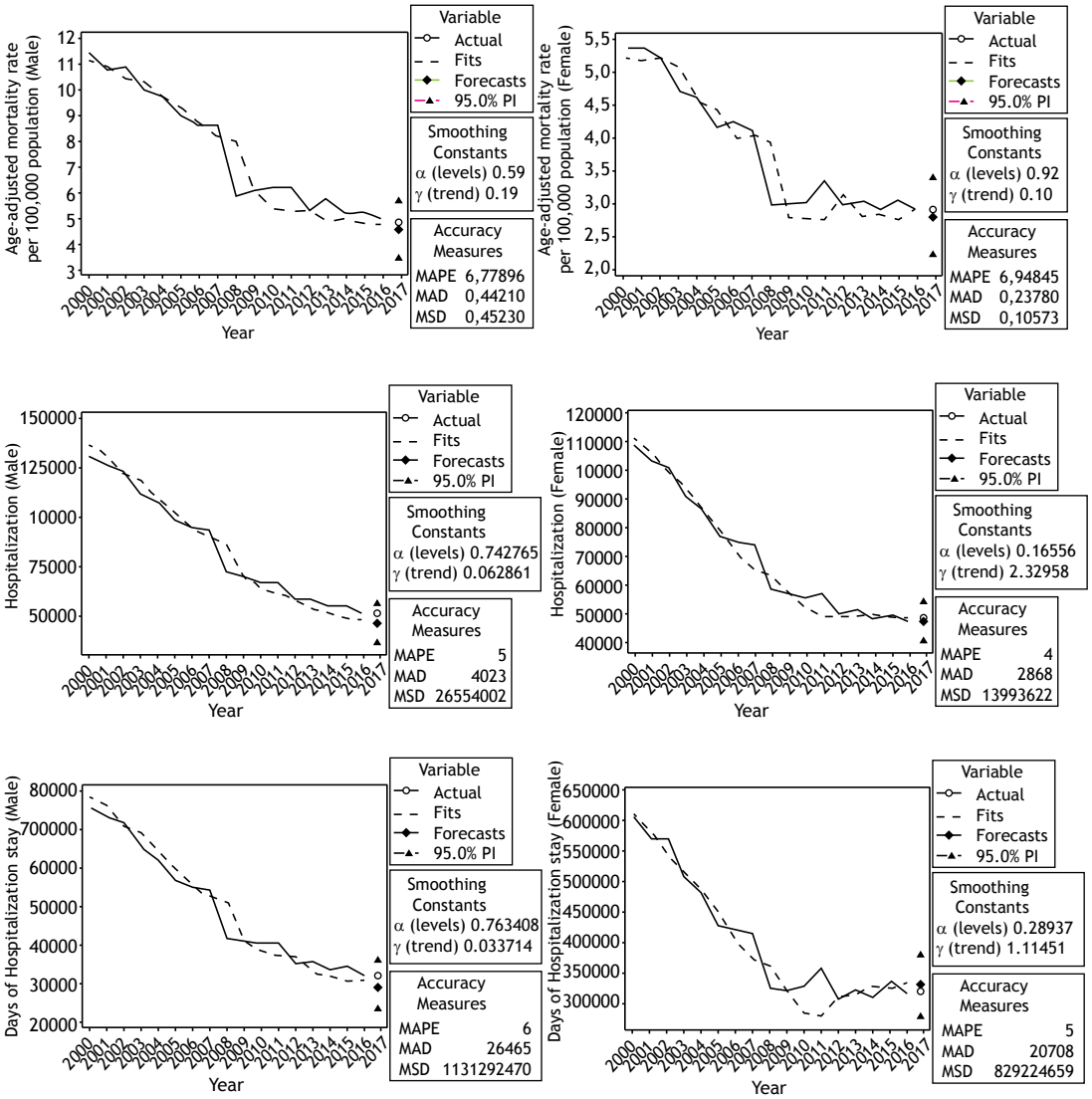

Figure 3. Double exponential smoothing model for age-adjusted in-hospital COPD mortality rates, number of COPD-related hospitalizations, and length of COPD-related hospital stays (in days) for females and males in Brazil, 2000-2016. MAPE: mean absolute percentage error; PI: prediction interval; MAD: mean absolute deviation; and MSD: mean squared deviation.

that Denmark is a country with an equitable health care system and better income distribution than that occurring in Brazil.[16] The decline in COPD mortality we observed in southern, southeastern, and central-western Brazil, in both genders and all age groups, also suggests a possible association between socioeconomic indicators and COPD mortality rates.

The decrease in in-hospital morbidity observed in all regions of Brazil might have been influenced by the availability of inhaled COPD medication at no charge from public health facilities. Since 2013, the federal government of Brazil has guaranteed the availability of short-acting and long-acting bronchodilators (adrenergic β_2 agonists and anticholinergics), as well as inhaled corticosteroids, a responsibility that was previously borne by the states.[27] In fact, several studies have demonstrated that regular use of inhaled medications reduces the number of exacerbations and hospitalizations due to COPD.[28-30] However, the fact that there was decline in in-hospital morbidity and mortality in the south, southeast, and central-west of Brazil supports the hypothesis that socioeconomic indices play a role in in-hospital COPD morbidity and mortality. In addition, if we consider that better socioeconomic conditions also have a positive influence on adherence to treatment in patients with chronic diseases, the findings of Tavares et al.[31] also validate our results. Those authors reported that individuals living in the south and southeast of Brazil are more likely to adhere to treatment.[31]

We also expected that the negative APCs for the number and duration of hospitalizations would be more pronounced in recent years. It is possible that the uneven distribution of inhaled COPD medication

Table 3. Comparison of values estimated by the predictive model for 2017, in relation to the values observed in the same year, for age-adjusted in-hospital mortality rate, number of hospitalizations and length of hospital stay for COPD in Brazil.

Variable	Actual	Forecast	Error (%)*	95% CI
Age-adjusted in-hospital mortality rate				
Male	4.98	4.61	7.43	3.53
Female	2.95	2.80	5.08	2.22
Hospitalizations				
Male	50,156	45,818	8.65	−55,673
Female	47,986	47,528	0.95	−54,554
Length of hospital stay (days)				
Male	327,355	301,384	7.93	−366,221
Female	322,894	330,940	2.49	−381,673

*((Actual − Forecast)/Actual) × 100.

throughout the country or discontinuity in its distribution during certain periods contributed to a less pronounced negative APC for the number of hospitalizations after 2009. The access to inhaled COPD medication at no charge provides the best control of the disease, which may have resulted in the hospitalization of only the more severe cases due to the natural evolution of the disease, as well as smoking-related comorbidities, consequently requiring longer hospital stays. Other factors, such as nonadherence to treatment, the increase in the life expectancy of the population in the last decade, and the ceiling effect of the drug distribution program—the greatest impact occurring in the first years of such programs—can also be considered to explain these findings.

Finally, the predictive models validated for the year 2017 demonstrated the ongoing downward trend in the in-hospital morbidity and mortality due to COPD in Brazil, although the amplitude of the confidence intervals enables higher estimates than those currently reported. The results of the present study could lay the groundwork for the development and validation of additional predictive models, controlling for socioeconomic indicators, which could increase the accuracy of the estimates.

This study has some limitations. First, we chose to use official data in the public domain, the source of which contains death certificates from the Brazilian National Ministry of Health Mortality Database, therefore being secondary data that are subject to inconsistencies and gaps. That data source does not present information regarding spirometry findings or the severity of COPD. Second, we did not have access to information on the use of inhaled COPD medications. That information is registered in the municipal pharmacies that are responsible for the distribution of such medications and is not in the public domain.

Our findings suggest that factors related to the distinct socioeconomic conditions observed in the various macro-regions of Brazil are involved in the control of COPD-related morbidity and mortality, as are factors already addressed in the literature, such as adherence to treatment and a reduction in smoking rates. It is possible that improving economic conditions will promote reductions in the rates of morbidity and mortality associated with COPD. Our predictive models could assist in decision making and in the planning of health policies for the treatment of COPD.

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Pulmonary function and functional capacity cut-off point to establish sarcopenia and dynapenia in patients with COPD

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ABSTRACT

Objective: To establish a cut-off point for clinical and functional variables to determinate sarcopenia and dynapenia in COPD patients, and to analyze the impact of skeletal muscle dysfunction (SMD) on these variables. **Methods:** Cross-sectional study, screened COPD patients for sarcopenia or dynapenia through low muscle mass and hand grip strength (HGS). Clinical variables: pulmonary function, respiratory muscle strength and functional capacity (FC). The precision of the variables in determining points of predictive cut-off for sarcopenia or dynapenia were performed using the Receiver Operating Characteristic curve and two-way analysis of variance. **Results:** 20 COPD patients stratified for sarcopenia (n = 11) and dynapenia (n = 07). Sarcopenia group presented lower lean mass and lower maximal inspiratory pressure (MIP), decreased HGS, reduced FC (p<0.050). Dynapenia group presented reduced MIP, lower HGS and walked a shorter distance at Incremental shuttle walk test (ISWT) (p<0.050). We found cut-off points of forced expiratory volume in one second (FEV_1), MIP and maximal expiratory pressure (MEP) and ISWT. It is possible to identify sarcopenia or dynapenia in these patients. We found the coexistence of the conditions (SMD effect) in COPD – reduction in the distance in the ISWT (p = 0.002) and %ISWT (p = 0.017). **Conclusion:** In moderate to very severe COPD patients the sarcopenia could be predicted by FEV_1 (%predicted) < 52, MIP < 73 cmH_2O, MEP < 126 cmH2O and distance traveled of < 295 m in ISWT. Whereas dynapenia could be predicted by FEV_1 < 40%, MIP < 71 cmH2O, MEP < 110 cmH2O and distance of < 230 m traveled in ISWT.

Keywords: Sarcopenia; Chronic obstructive pulmonary disease; Musculoskeletal system.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a persistent airflow limitation initially associated with abnormal inflammatory response in the airways and lungs.[1] Secondarily, its progression reflects on multisystemic symptoms and the presence of comorbidities such as skeletal muscle dysfunctions (SMD), obstructive sleep apnea, cardiovascular disease, metabolic syndrome, osteoporosis, mental disorders and lung cancer.[2,3] Systematic inflammation in COPD increases the presence of inflammatory mediators on bloodstream, promoting oxidative stress, consequently resulting on protein degradation, causing SMD.[4-6] Nutritional imbalance and hypoxemia are also potential contributors for this condition, which results in a poor prognosis independent of lung function.[7]

SMD is composed by peripheral muscle weakness, a shift from type I and II to a higher presence of type II fibers and muscular atrophy. COPD patients usually have decreased tolerance to physical exercise and difficulties in performing activities of daily living. Hence studying skeletal muscle function, structure and its dysfunction in this population is important because its repercussions bring to low exercise performance, poor health status and premature mortality.[7,8]

Age-related loss of muscle strength is known as dynapenia,[9] which leads to functional impairment of the skeletal muscle system and is associated with diminished physical performance.[10] Loss of skeletal muscle mass is referred as sarcopenia[11] and its etiology could have genetic, physiological, and environmental factors.[12] It is noteworthy that there is no global consensus on the term sarcopenia.[13] Both conditions are linked to reduction in muscle performance leading to exercise intolerance and sedentary behaviors.[14] It is already known that sarcopenia could coexist with

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other disorders,[15] but the presence and prevalence of the overlapping between dynapenia and sarcopenia is still unknown.

The prevalence of sarcopenia in stable COPD patients is around 15%, which increased with age and GOLD stages.[16] The prevalence of dynapenia in COPD patients needs to be investigated. It is important to emphasize that COPD is characterized by two different phenotypes that have their own particularities, which we should take in account when thinking on how much sarcopenia and dynapenia are related to these phenotypes.[17] Therefore, our aim was to establish a cut-off point for clinical and functional variables to determinate sarcopenia and dynapenia in COPD patients and to analyze the impact of skeletal muscle dysfunction on the evaluated variables. We hypothesized that in COPD patients, sarcopenia and dynapenia could be predicted by reduced functional capacity, respiratory muscle strength and airway obstruction.

METHODS

Study design

This was a cross-sectional study performed on a convenience non-probability sample, conducted in the Santa Cruz Hospital's Cardiorespiratory Rehabilitation Program (Santa Cruz do Sul, RS, Brazil). The sample of our study was constituted of patients who attend the pneumology outpatient clinic of the Santa Cruz Hospital for follow-up and treatment of their conditions and were requested to join the Cardiorespiratory Rehabilitation Program through the pulmonologist or general practitioner referral. The Research was approved by the Research Ethics Committee of University of Santa Cruz do Sul, protocol n. 1.514.705. All volunteers signed an informed consent statement prior to participation.

Subjects and selection

Subjects with clinical diagnosis of COPD confirmed by pulmonary function test, adequate cognition, no disease exacerbation 30 days prior to the study who signed the informed consent statement were included in the study. The exclusion criteria were musculoskeletal or neurological disorders that affected the locomotor system in such a way that would impede participation in the research protocol, clinical diagnosis of lung cancer, current alcoholism, arrhythmias, uncontrolled metabolic disease, or electrocardiogram alterations.

Measurements

The research was conducted in an acclimated laboratory at a temperature of 22 °C and relative humidity between 50% and 60%, during the morning (between 8 a.m. to 12 a.m.). Subject's clinical characteristics were reviewed and recorded including age, sex, height, weight and medications used.

Dynapenia screening

Hand-grip strength (HGS) was measured to evaluate muscle strength (Jamar Hydraulic Dynamometer, Bolingbrook, IL, USA). To perform the maneuver, volunteers were sitting on a standard height chair without armrest with their shoulder adducted, elbow flexed at 90°, forearm in neutral position, and wrists with 15° extension.[18] Participants were asked to grasp the dynamometer at their maximal power. Three attempts on both hands were performed with a one-minute rest between each of them. The mean value of each hand was used in the analysis. We considered dynapenia when our patients presented cut-off values of < 30 kg/f for men and < 20 kg/f for women.[19]

Sarcopenia screening

The skeletal muscle mass was assessed by the appendicular skeletal muscle mass (ASM) and defined skeletal muscle mass index (SMI) as ASM/height^2 (kg/m^2).[20] Sarcopenia was diagnosed according to the criteria proposed by the European Working Group for Sarcopenia in Older People.[11] Were considered sarcopenic those patients with low muscle mass defined as SMI below 7.26 kg/m^2 for men and below 5.45 kg/m^2 for women.[11]

To evaluate the lean mass, patients' body composition was assessed by means of electrical bioimpedance with Biodynamics® (model 420, international version 5.1). The exam was performed according to the National Institutes of Health Technology Assessment Conference statement.[21]

Pulmonary function test

To assess pulmonary function a digital spirometer (Microloop®, MK8, Care Fusion, Hoechberg, Germany) was used. The test was performed in accordance to the American Thoracic Society recommendations,[22] and the results were interpreted according to the values predicted by Pereira et al.[23] The variables analyzed were: forced expiratory volume in 1 s (FEV_1), and the FEV_1/FVC ratio. Airflow limitation was categorized in agreement to the Global Initiative for Chronic Obstructive Lung Disease 2018 recommendations, where patients were classified as mild (GOLD I), moderate (GOLD II), severe (GOLD III), or very severe (GOLD IV).[1]

Respiratory muscle strength

Respiratory muscle strength (RMS) was evaluated through digital manometer (MDI®, MVD300, Porto Alegre, Brazil), where we obtained measures of the maximum inspiratory pressure (MIP) and the maximum expiratory pressure (MEP). MIP was obtained after the individual expired to the residual volume and carried out the inspiration until total lung capacity. For the measurement of the MEP, the patient underwent an inspiration to total lung capacity, expiring until the residual volume. The values were later compared with those described in the literature for Brazilian population[24] and expressed as a percentage of predicted values.

Respiratory muscle weakness was determined for a MIP of < 60 cmH_2O.[25]

Functional capacity

The incremental shuttle walking test (ISWT) aims to assess one's performance considering the individuals' limiting symptoms used to evaluate functional capacity as described in Singh et al.[26] The test has 12 stages with one minute each, with initial velocity of 0.5 m/s, with each minute being added 0.17 m/s (equivalent to 10 m/min). There was provided a standardized verbal command at the end of each stage to inform the individual of increasing walking speed. The walking speed is determined by two distinct types of beeps: a single beep indicating a change of direction, and a triple (beep) signal that indicates a change of direction and stage. The percentage of the predicted walked distance ISWT (% predicted) was calculated considering sex, age, height and weight of each patient according to Dourado et al.[27]

Statistical analyses

Data were analyzed using the Sigmaplot® statistical package (version 11.0, Systat Software Inc., San Jose, CA, USA). Data were tested for normality through the Shapiro-Wilk test and presented descriptively as mean and STD (parametric) or as median and minimum and maximum interval (non-parametric). The analyses between the groups were performed through Student T test or Mann Whitney.

The precision of the clinical variables, pulmonary function (FEV_1% predicted), respiratory muscle strength (MIP) and functional capacity (ISWT) in determining points of predictive cut-off sarcopenia and dynapenia were performed using the Receiver Operating Characteristic (ROC) curves.[28] The total area under the ROC curve was determined between FEV_1 (% predicted), MIP, ISWT, and sarcopenia and dynapenia indexes. The greater area under the ROC curve represented greater discriminatory power of clinical variables to establish sarcopenia or dynapenia in individuals with COPD.[29] The 95% confidence interval (95% CI) was used to determine the ability of the clinical variables to predict sarcopenia and dynapenia, with the lower limit being greater than 0.50.[24] Subsequently, the cut-off points of the clinical variables that obtained significant areas under the ROC curve, with the respective values of sensitivity and specificity, balanced among themselves. Values lower than 60% were identified.

The results were compared using two-way analysis of variance on ranks with post-hoc Bonferroni, in order to identify statistically significant differences in: (i) functional capacity; and (ii) pulmonary function. For these analyses, subjects were categorized according to SMD effect (dynapenia *vs* sarcopenia) and Non SMD effect (non dynapenia *vs* non sarcopenia). Residuals were evaluated under the assumptions of normality, constant variance, and independence. $P \leq 0.05$ was considered significant.

RESULTS

A total of 20 subjects were enrolled in the study. Of them, 11 were stratified with sarcopenia, 7 with dynapenia and 7 with overlapping between the conditions. In COPD patients with sarcopenia there were found lower lean mass and lower MIP, decreased HGS and reduced functional capacity than non-sarcopenia group. The patients with dynapenia presented reduced MIP, lower HGS and walked a shorter distance in the ISWT, when compared with non-dynapenia group (Table 1). There were no significant differences of the groups for age, BMI, pulmonary function, GOLD stages and MEP. It is important to highlight that we did not find any significant difference between overlapping and dynapenia and sarcopenia groups in isolation.

The cut-off points, the areas under the ROC curve and 95% CI of clinical variables, as well as the sensitivity and specificity of the clinical variables as predictors of sarcopenia and dynapenia are showed in Table 2. According to the prediction model, FEV_1 < 52%, MIP < 73 cmH_2O, MEP < 126 cmH_2O identified sarcopenia in these patients and FEV_1 < 40%, MIP < 71 cmH_2O, MEP < 110 cmH_2O identified dynapenia. The distance walked on the ISWT was significantly able to determine the presence of sarcopenia and dynapenia in patients with COPD, with walked distance of 295 and 230 m respectively. There was established as cut-off point according to the adopted sensitivity and specificity.

When applying two-way ANOVA, there was found that COPD patients with dynapenia and sarcopenia (SMD effect) presented a reduction in the distance walked in the ISWT ($p = 0.002$) and the %ISWT ($p = 0.017$) (Figure 1), demonstrating the impact of SMD on the functional capacity of these patients. We emphasize that there were not significant results for FEV_1.

DISCUSSION

COPD patients with sarcopenia or dynapenia present reduced inspiratory muscular strength, handgrip strength and distance walked in the ISWT. COPD patients with sarcopenia also presented a reduction in lean mass. According to ROC curve, it was possible to establish that COPD patients with FEV_1 (%pred) < 52%, MIP < 73 cmH_2O, MEP < 126 cmH_2O identified sarcopenia; and FEV_1 < 40%, MIP < 71 cmH_2O, MEP < 110 cmH_2O identified dynapenia. Furthermore, a distance walked in the ISWT of 295 and 230 m can determine sarcopenia or dynapenia, respectively.

SMD is associated with diminished physical performance and functional capacity. Moreover, skeletal muscle impairment could provoke physiological, metabolic and functional repercussions.[30,31] In COPD patients, the SMD affects both ventilatory and non-ventilatory muscle groups, contributing to greater energy expenditure for the individual to execute his activities of daily living, it also leads to decreased quality of life and the aftermath is a poor prognosis.[3] Our study is in congruence with these findings, where we found an impact on handgrip and respiratory muscle strength

Table 1. COPD patients' clinical characteristics stratified by sarcopenia and dynapenia.

Variables	Non-Dynapenia (n = 13)	Non-Sarcopenia (n = 9)	Dynapenia (n = 7)	Sarcopenia (n = 11)	Dynapenia + Sarcopenia (n = 7)	P#	P*
Age (years)	65.0±4.0	65.6±5.1	66.5±4.1	65.7±5.0	65.0±5.3	0.34	0.98
Sex, Male n (%)	11 (84.6)	6 (66.6)	4 (57.1)	10 (90.9)	5 (71.4)	0.30	0.26
Height (cm)	1.5±0.1	1.6±0.1	1.6±0.3	1.6±0.1	1.6±0.1	0.85	0.86
BMI (Kg/m²)	26.0±6.6	25.7±5.6	24.6±4.9	25.5±6.6	25.9±3.4	0.48	0.73
Lean Mass (Kg)	43.9±15.0	53.9±12.8	37.8±6.6	34.2±6.9	30.1±5.3	0.02	0.20
Spirometrics							
FEV_1 (L/s)	1.1±0.7	1.2±0.6	0.9±0.1	0.9±0.4	1.0±0.5	0.09	0.53
FEV_1 (%predicted)	38.3±24.1	44.8±23.6	37.6±11.0	33.6±18.3	39.1±18	0.10	0.88
FEV_1/FVC (L/s)	0.50±0.16	0.53±0.19	0.44±0.13	0.44±0.11	0.44±0.13	0.26	0.44
FEV_1/FVC (%predicted)	64.4±23.6	68.8±28.2	56.7±17.1	57.3±16.0	56.7±17.1	0.26	0.42
Staging (GOLD) COPD, n (%)						0.60	0.35
Stage II	5 (38.4)	4 (44.4)	1 (14.2)	2 (18.1)	1 (14.3)		
Stage III	4 (30.7)	2 (22.2)	4 (57.1)	4 (36.3)	4 (57.1)		
Stage IV	4 (30.7)	3 (33.3)	2 (28.5)	5 (45.4)	2 (28.6)		
Respiratory muscle strength							
MIP (cmH_2O)	78.2±27.6	82.3±18.0	52.1±21.8	62.4±31.4	67.5±27.1	0.04	0.03
MIP (% predicted)	79.5±29.1	86.0±18.2	55.9±24.9	63.3±30.6	70.5±28.5	0.20	0.73
MEP (cmH_2O)	114.8±43.6	124.1±32.5	89.1±33.1	95.8±44.5	101.8±32.5	0.15	0.26
MEP (% predicted)	106.3±36.0	121.2±26.7	90.2±34.8	88.3±35.2	95.1±18.5	0.10	0.35
Inspiratory Muscle Weakness (MIP < 60 cmH_2O), n (%)						0.06	0.04
Yes	1 (7.6)	1 (11.1)	5 (71.5)	7 (63.7)	5 (71.4)		
No	12 (92.4)	8 (88.9)	2 (28.5)	4 (36.3)	2 (28.6)		
Hand Grip Strength							
Hand Grip (kg/f)	39.2±10.0	37.7±12.9	21.0±5.1	31.1±11.3	22.3±5.4	0.04	<0.01
Functional capacity							
ISWT (m)	326.1±77.5	347.5±57.7	251.6±77.8	270.0±86.0	215.7±118.7	0.02	0.03
ISWT (% predicted)	47.9±16.0	55.4±13.3	38.3±9.3	37.2±10.7	33.9±16.9	0.05	0.16

Data are presented as mean ± standard deviation; n (%): number of patients (% of sample size); P# < 0.050 between sarcopenia vs no sarcopenia; P* < 0.050 between dynapenia vs non dynapenia; COPD: Chronic Obstructive Pulmonary Disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Lung Disease; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; ISWT: incremental shuttle walking test.

Table 2. Cut-off values, sensitivity and specificity of variable clinics with prediction of sarcopenia and dynapenia in COPD patients.

Variables	Sarcopenia (n = 20)				Dynapenia (n = 20)			
	Cut-off	Sensitivity	Specificity	AUC [Interval Confidence 95%]	Cut-off	Sensitivity	Specificity	AUC [Interval Confidence 95%]
Spirometrics								
FEV_1 (L/s)	1.0	75	71	0.726 [0.477-0.902]	0.97	57	50	0.580 [0.336-0.798]
FEV_1(% predicted)	0.52	83	57	0.738 [0.489-0.909]	0.40	57	41	0.580 [0.336-0.798]
Respiratory muscle strength								
MIP (cm H_2O)	73	66	85	0.696 [0.447-0.882]	71	62	72	0.545 [0.305-0.771]
MIP (% predicted)	70	66	85	0.690 [0.441-0.878]	70	71	67	0.534 [0.295-0.762]
MEP (cm H_2O)	126	58	43	0.649 [0.400-0.850]	110	50	72	0.597 [0.351-0.811]
MEP (% predicted)	100	66	85	0.750 [0.502-0.917]	101	75	72	0.659 [0.410-0.857]
Functional capacity								
ISWT (m)	295	66	85	0.774 [0.527-0.931]	230	71	80	0.855 [0.592-0.977]
ISWT (% predicted)	45	75	71	0.774 [0.527-0.931]	45	71	58	0.532 [0.288-0.766]

COPD: Chronic Obstructive Pulmonary Disease; AUC: Area under curve; FEV_1: forced expiratory volume in 1 s; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; m: meters; n: number of patients; ISWT: incremental shuttle walk test. Statistical significance p < 0.05.

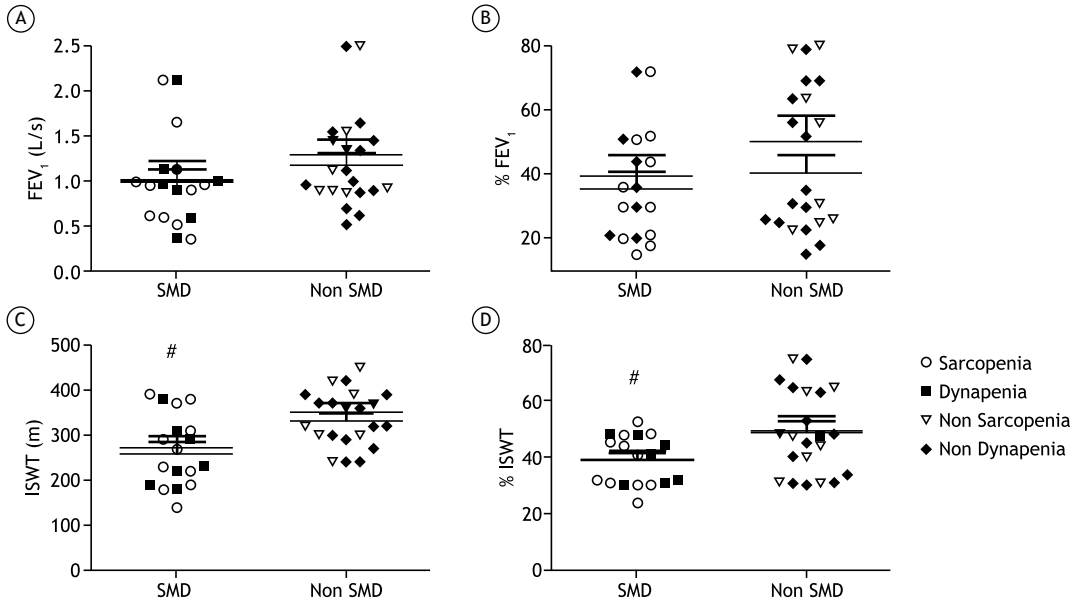

Figure 1. Comparison of functional capacity and FEV_1 in COPD patients with MSD and without MSD. #p <0.050 for MSD. FEV_1: forced expiratory volume in one second; ISWT: Incremental shuttle walk test; MSD: muscular skeletal dysfunction. (A) Comparison between FEV_1 (L/s) of MSD and non-MSD groups; (B) Comparison between% FEV_1 of MSD and non-MSD groups; (C) Comparison between ISWT (m) of MSD and non-MSD groups; (D) Comparison between% ISWT of MSD and non-MSD groups.

as well as in functional capacity on both patients with sarcopenia or dynapenia.

SMD pathophysiology is complex and involves fiber damage and catabolic events that worsen with ageing and the presence of comorbidities.[30] Byun et al.[4] found correlation between sarcopenia, old age, low body mass index, presence of comorbidities and systemic inflammation in COPD patients. Therefore, considering that our sample was composed by elderly subjects, we can hypothesize that muscle wasting in our patients was due to natural physiological reasons, like an imbalance between muscle protein synthesis and muscle protein breakdown and changes associated with COPD consequences, such as chronic inflammation and functional decline. It is important to emphasize that the loss of 1% of lean mass is equivalent to a reduction of 3% in muscle strength in elderly, something that could have an impact on one's functionality.[27]

Sarcopenia and dynapenia are two conditions related to muscle mass and its function, and for identifying them there are several methods that could be used. Bone et al.,[31] in a review paper, listed handgrip strength and low gait speed as instruments for defining sarcopenia. Handgrip measurement has the advantage of being simple and easy and sometimes used as an index of muscular strength for the whole body. When it comes to muscle mass evaluation we used bioelectrical impedance analysis, considered by Maddocks et al.[32] a more practical tool for this purpose. There are other methods used for muscle mass assessment as seen in Bone et al.,[31] who cited dual X-ray absorptiometry and computational tomography. Specifically to determinate dynapenia, Morley et al.[33] mentioned evaluating walking speed, walking distance and stair climbing as screening tools. Whilst for identifying sarcopenia in COPD patients, most studies used Six-minute walk test for functional capacity evaluation, to our knowledge no study has used ISWT for this purpose.[34-36]

To date, there is still no consensus on measurement tools or diagnostic cut-off to determinate these two conditions, but it is known that diagnosis could be done by assessing muscle mass and functional performance.[5] The diversity of methods available to measure these variables could lead to several cut-off as well underestimate the presence of this condition in COPD patients. We emphasize that this is a relevant and original study where we evaluated sarcopenia and dynapenia in moderate to very severe COPD patients. With a pulmonary function test, through FEV_1 (%pred) < 52 and assessing physical performance by means of ISWT, the distance traveled of < 295 m is able to predict sarcopenia, and a distance in ISWT of < 230 m is able to predict dynapenia.

Our findings are important because they allow clinical practitioners to apply feasible methods to assess sarcopenia and dynapenia on their routine, like a spirometry and a 10 m hall to perform ISWT. Additionally, the results demonstrate that a careful evaluation of these patients is required, as well as a future focus on SMD based mechanisms and its relationship with activity of daily living execution, physical activity levels and quality of life in a COPD population.

Some limitations pointed out are due to our strict inclusion and exclusion criteria, resulting in a number of

subjects that might be considered small. We emphasize that our results should be considered only for patients with COPD. This study is of clinical relevance since SMD in COPD impacts on anatomical, physiological and functional systems. Identifying these conditions could help health care professionals to assess in a feasible and workable way, to understand and treat patients with specifically interventions (e.g multidisciplinary rehabilitation programs), it is already known that physical exercise can reverse sarcopenia in COPD patients and improve the condition in older adults[37]. Regarding nutritional treatment strategies there is still a lack of specific recommendations.[38] Knowing that skeletal muscles perform essential functions for the whole organism, we highlight the importance of early recognition of these disorders for patients' risk stratification and prevention, which may reduce the development of comorbidities, delay functional decline and improve prognosis in patients with chronic obstructive pulmonary disease.

In conclusion, this study was able to give variables' cut-off points for identifying or predicting sarcopenia and dynapenia in moderate to very severe COPD patients. Moreover, these SMD cause negative impact on the peripheral muscular strength and functional capacity. Sarcopenia could be predicted by FEV_1 (%predicted) < 52, MIP < 73 cmH_2O, MEP < 126 cmH_2O and distance traveled of < 295 m in ISWT. Whereas, dynapenia could be predicted by FEV_1 < 40%, MIP < 71 cmH_2O, MEP < 110 cmH_2O and distance of < 230 m traveled in ISWT.

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Cross-cultural adaptation of the Cambridge Pulmonary Hypertension Outcome Review for use in patients with pulmonary hypertension in Colombia

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ABSTRACT

Objective: To conduct a cross-cultural adaptation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) as an instrument to evaluate the perception of symptoms, functional limitation, and health-related quality of life (HRQoL) in subjects diagnosed with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) in Colombia. **Methods:** The adaptation process involved 3 phases: translation, cognitive debriefing interviews, and a validation survey. To evaluate the psychometric properties, we recruited individuals ≥ 18 years of age who had been diagnosed with PAH or CTEPH to take part in the latter two stages of the adaptation process. All individuals were being followed on an outpatient basis by the pulmonary hypertension programs at *Hospital Universitario San Ignacio, Fundación Clínica Shaio,and Clínicos IPS*, all located in the city of Bogotá, Colombia. **Results:** A Spanish-language version of the CAMPHOR was developed for use in Colombia. The internal consistency was excellent for the symptoms, functioning, and quality of life scales (Cronbach's alpha coefficients of 0.92, 0.87, and 0.93, respectively). Test-retest reliability was above 0.70. The evaluation of the convergent validity and known group validity of the CAMPHOR scales confirmed that there were moderate and strong correlations with the related constructs of the Medical Outcomes Study 36-item Short-Form Health Survey, version 2, as well as showing their capacity to discriminate disease severity. **Conclusions:** The Spanish-language version of the CAMPHOR developed for use in Colombia was the result of a translation and cultural adaptation process that allows us to consider it equivalent to the original version, having shown good psychometric properties in the study sample. Therefore, its use to assess the impact of interventions on the HRQoL of patients with PAH or CTEPH is recommended, in research and clinical practice.

Keywords: Quality of life; Hypertension, pulmonary; Pulmonary embolism; Psychometrics.

INTRODUCTION

Pulmonary hypertension (PH) is a common hemodynamic condition defined by a mean pulmonary artery pressure greater than or equal to 25 mmHg, as determined by right heart catheterization.[1]

PH accompanies multiple pathological conditions, which are classified into 5 large groups according to the physiopathological mechanism involved[2]:

1. Pulmonary arterial hypertension (PAH)
2. PH associated with left heart disease
3. PH associated with lung disease and/or hypoxia
4. Chronic thromboembolic PH (CTEPH)
5. PH associated with multifactorial mechanisms

The most common causes of PH are group 2 and group 3 conditions, in which PH confers a worse prognosis despite its mild severity and slow progression. When PH belongs to group 2 or group 3, it is not considered a separate disease, and, therefore, treatment is that of the underlying disease.[3]

In contrast, PAH and CTEPH (groups 1 and 4) are considered to be uncommon (5% and 4%, respectively), high mortality diseases of the pulmonary circulation, resulting from pulmonary vascular remodeling and vascular bed obstruction, which, over time, cause right ventricular dysfunction and failure.[1,3,4]

Knowledge of pathophysiological mechanisms has made it possible to change the clinical course of a disease that had a mean survival of 2.8 years and have multiple therapeutic options that can increase life expectancy, restore exercise tolerance, improve the

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hemodynamic profile, and improve health-related quality of life (HRQoL).[3-6]

Most medications for treating PAH and CTEPH have been demonstrated to be effective and safe on the basis of endpoints such as increases in six-minute walk distance, improvements in hemodynamic parameters, improvements in functional class, and reductions in biomarkers (natriuretic peptide).[3,6-11] Those endpoints have been shown not necessarily to correlate with improvements in symptoms, HRQoL, or life expectancy; therefore, experts recommend that endpoints that directly evaluate morbidity/mortality and improvements in HRQoL be considered, so that new molecules can be approved and included.[12,13]

There is a significant impact on HRQoL in patients diagnosed with PAH or CTEPH,[14,15] as a result of the physical and functional limitations of the disease, comorbidities, and the therapy used.

This impact on HRQoL has been described using tools such as the Borg scale, the Saint George's Respiratory Questionnaire, the Minnesota Living with Heart Failure Questionnaire, the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), the Nottingham Health Profile, the European Quality of Life-5 Dimensions questionnaire,[15] and emPHasis-10.[16] Until recently, the first and only questionnaire developed specifically to assess HRQoL in PH was the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).[17] This self-administered tool developed in the United Kingdom was the result of in-depth interviews conducted with patients with PH and has 3 scales: symptoms (25 questions); functioning (15 questions); and quality of life (25 questions)—with higher scores corresponding to a greater impact of the disease on patient HRQoL.

The CAMPHOR has been demonstrated to be a tool that yields valid, reliable, and sensitive results for evaluating baseline HRQoL and post- intervention HRQoL in subjects with PAH or CTEPH,[15,17,18] and, therefore, it has undergone several semantic and cultural adaptation processes, all of which resulted in versions with good psychometric properties, similar to those of the original version.[19-26]

The CAMPHOR has been adapted and validated for use in the United States,[19] Canada,[20] Australia/New Zealand,[21] Germany/Switzerland/Austria,[22] Sweden,[23] Portugal,[24] the Netherlands,[25] and recently in Spain,[26] with all versions having good psychometric properties.

Currently in Colombia, there is no instrument that allows us to evaluate the perception of patients with PAH or CTEPH regarding the effects of the disease on different aspects of their lives, which we consider essential for providing comprehensive treatment and the necessary support for each patient. Therefore, the main objective of this study was to conduct a cultural (semantic and psychometric) adaptation of the CAMPHOR as an instrument to measure the perception of symptoms, functional limitation, and HRQoL in subjects diagnosed with PAH or CTEPH in Colombia.

METHODS

This study was approved by the Research Ethics Committees of *Hospital Universitario San Ignacio*, *Fundación Clínica Shaio*, and *Clínicos IPS*, all of which are located in the city of Bogotá. The adaptation process to develop a Spanish-language version of the CAMPHOR for use in Colombia consisted of 3 phases: translation of the questionnaire; cognitive debriefing interviews; and a validation survey. Patients were invited to participate in phases 2 and 3 if they were ≥ 18 years of age, had been diagnosed with PAH or CTEPH, and were able to complete the forms.

The CAMPHOR was translated using the two-panel method,[27] which consisted, first, of a bilingual panel, which was responsible for producing a first Spanish-language version of the questionnaire; was formed of local individuals, who were fluent in English and Spanish and had no history of professional clinical practice; and was accompanied by a representative of Galen Research (the holders of the intellectual property of the CAMPHOR). Second, a lay panel was formed including local individuals with an average level of education and no knowledge of English, who were responsible for determining whether the phrasing and the words chosen for each item in the translated version were acceptable and sounded natural.

Face-to-face semi-structured interviews were conducted in accordance with a protocol provided by Galen Research, in which respondents filled out the questionnaire, while a researcher observed the uncertainties created by the items and subsequently asked respondents about item comprehensibility and aspects of living with PH. The objective of those interviews was to evaluate the applicability, relevance, comprehensibility, semantic equivalence, and technical equivalence of the Spanish-language version of the CAMPHOR developed by the two panels for use in Colombia.

The Spanish-language version of the CAMPHOR developed for use in Colombia underwent a psychometric evaluation to determine whether the results obtained were reliable, consistent, and valid. The instrument was administered twice (test-retest), approximately two weeks apart, to 81 patients who met the selection criteria and were recruited by convenience sampling.

Descriptive statistics for continuous variables are expressed as mean (standard deviation), median (interquartile range), and percentage of patients scoring the minimum and maximum possible scores.[28,29] Internal consistency was evaluated by using Cronbach's alpha coefficient, for which a value greater than 0.70 is evidence of satisfactory reliability and indicates an appropriate relationship of the items with one another, allowing their combination into a scale. Spearman's correlation coefficient was

calculated in order to evaluate the reliability of the scales over time (test-retest). A value greater than or equal to 0.70 indicates a low degree of random error in measurement of the new Spanish-language version of the instrument.

Convergent validity was determined by evaluating the level of association between the CAMPHOR and SF-36v2 scale scores for the first administration (T1), by using Spearman's correlation coefficient. Although higher scores on the SF-36v2 indicate better health status, the same is not true for CAMPHOR scores.

In order to determine known group validity, the factor used was perceived symptom severity. Nonparametric tests for independent samples (Mann-Whitney U test) were used to test differences in the CAMPHOR scores between the groups. Values of $p < 0.05$ were considered statistically significant.

RESULTS

A bilingual panel consisting of 6 women between 33 and 54 years of age, who were fluent in English and had no history of clinical practice, translated the original English-language version of the CAMPHOR into Spanish. In general, the panel considered that the instructions and most of the questions were clear and easy to translate. Translation alternatives for each item were discussed until consensus on conceptual equivalence was achieved, and more than one alternative was provided for some items so that the lay panel could choose among them. Two items with significant colloquial components (#23 in the symptoms scale ["I feel hopeless"] and #10 in the quality of life scale ["It feels like my body has let me down"]) were found hard to translate because of difficulties in conveying the idea of the original language ("hopelessness" and "disappointment with one's body") into Spanish. The translation sought to maintain conceptual equivalence, and the lay panel selected the best alternative for each one.

The lay panel (which consisted of 3 women and 2 men who were between 25 and 53 years of age and had no knowledge of English) was responsible for reviewing the translations, that is, the phrasing and language used, as well as for selecting among the translation alternatives proposed by the bilingual panel those that were most appropriate. Some minor changes were made to three of the items to facilitate comprehension and make them sound more natural in Spanish in Colombia.

After the version of the instrument had been developed and consolidated by the two panels, in-depth interviews were conducted with 11 subjects diagnosed with PAH or CTEPH. The subjects completed the questionnaire in a mean time of 11 minutes (standard deviation ± 3). During the interviews, difficulties were identified for the YES/NO response options in the section on quality of life because the NO option created a double negative in the item, and, therefore, the response options were changed to True/False. However, the questionnaire was considered understandable, clear, and easy to complete.

Psychometric evaluation was performed with 81 subjects diagnosed with PAH or CTEPH. The questionnaire was administered at 2 time points 15 days apart (T1 and T2). In addition to the CAMPHOR, participants completed the SF-36 version 2 (SF-36v2) at one time point (T1).

The demographic characteristics of participants are presented in Table 1. The mean age of subjects was 49 ± 15 years, with females predominating (female-to-male ratio, 5:1), and, although most subjects described the severity of their hypertension as moderate-severe (79%), it is striking that one third of them were still occupationally active (27%) or still performed household chores (37%).

The scores on the Spanish-language version of the CAMPHOR developed for use in Colombia, at T1 and T2, as well as the SF-36v2 scale scores at T1, are presented in Table 2. High ceiling effects were observed for some SF-36v2 scales (i.e., a large number of patients scored the maximum score), which could suggest that this measure of health status is not suitably targeted at patients with PH. In contrast, for the CAMPHOR, there was no evident ceiling or floor effect (i.e., less than 10% reached the minimum or maximum score).

Cronbach's alpha coefficients for internal consistency are shown in Table 3. For all CAMPHOR scales, Cronbach's alpha coefficients were above 0.80, indicating a good interrelationship among the items in each scale.

For the sake of reproducibility, patients who reported or experienced a change in their perception of their disease severity between T1 and T2 were excluded from the analysis. The test-retest reliability (Table 4) for each of the 3 CAMPHOR scales (symptoms, functioning, and quality of life) showed a strong correlation (0.79; 0.79, and 0.84, respectively) and was close to the value of 0.85 found in the study that developed the original instrument. The stable values observed result in low likelihood of random error in measurement, adjusting for changes in patient health status over time. The values obtained for the CAMPHOR scales are markedly higher than those obtained for other instruments.

Table 5 shows the correlations between the CAMPHOR and SF-36v2 scales at T1. As expected, the CAMPHOR symptoms and functioning scales had strong correlations with the SF-36v2 physical functioning and role-physical scales, respectively. The CAMPHOR quality of life scale score had moderate to strong associations with the SF-36v2 scale scores, which indicates that many factors influence quality of life.

For known-group analysis, perceived disease severity was classified as "Mild/Moderate" and "Fairly severe/Very severe" because of the small number of subjects belonging to the "Mild" and "Very severe" groups. Figure 1 shows the differences in CAMPHOR

Table 1. Demographic characteristics of participants.[a]

Variable	Cognitive debriefing interviews (n = 11)	Validation survey (n = 81)
Age, years	38 ± 16	49 ± 15
Range	18-69	18-79
Gender		
Female	9 (82)	68 (84)
Male	12 (18)	13 (16)
Marital status		
Single	5 (45)	25 (31)
Married/steady partner	6 (55)	46 (57)
Divorced	0 (0)	8 (10)
Widowed	0 (0)	2 (2)
Work activity		
Works full time	5 (45.0)	10 (12.3)
Works part time	0 (0)	12 (14.8)
Housewife	0 (0)	30 (37)
Pensioner	2 (18.0)	18 (22.2)
Retired due to illness	1 (9.0)	4 (4.9)
Unemployed	1 (9.0)	3 (3.7)
Student	1 (9.0)	2 (2.5)
Other	1 (9.0)	2 (2.5)
PH severity		
Mild	1 (9.0)	10 (12)
Moderate	4 (36.0)	33 (40.7)
Severe	5 (45.0)	31 (38.3)
Very severe	1 (9.0)	6 (7.4)

[a]Values expressed as mean ± SD or as n (%).

Table 2. Questionnaire descriptive scores (time points 1 and 2).

Questionnaire	n of patients	Median score (IQR)	Min-max possible score	% of patients scoring the minimum score	% of patients scoring the maximum score
CAMPHOR (T1)					
Symptoms	80	8 (5-13)	0-24	3.7	0
Functioning	81	9 (5-14)	0-26	4.9	0
Quality of life	81	5 (3-13)	0-22	7.4	0
CAMPHOR (T2)					
Symptoms	77	7 (3-13)	0-23	2.5	0
Functioning	77	10 (6-15)	0-25	4.9	0
Quality of life	77	5 (2-12)	0-24	6.5	0
SF-36v2 (T1)					
Physical functioning	79	50 (30-65)	5-100	0	3.7
Role-physical	79	56 (38-81)	0-100	2.5	12.3
Bodily pain	79	51 (41-72)	0-100	2.5	14.8
General health	79	50 (35-67)	5-100	0	1.2
Vitality	79	56 (44-75)	6-100	0	7.4
Social functioning	79	75 (50-100)	13-100	0	32.1
Role-emotional	79	83 (50-100)	0-100	3.7	43.2
Mental health	79	75 (55-95)	15-100	0	21.0

IQR: interquartile range; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; T1: time point 1; T2: time point 2; and SF-36v2: Medical Outcome Study 36-Item Short Form Health Survey, version 2

scale scores by disease severity group, with patients with more severe PH scoring higher on each scale. Each scale of the Spanish-language version of the CAMPHOR developed for use in Colombia was able to distinguish between patients according to disease severity.

DISCUSSION

The process of adapting an instrument prepared in one language and culture for use in another is a major methodological challenge in which, in addition to making an equivalent translation, it is necessary to conduct a psychometric evaluation process that can ensure that the instrument and the constructs that it tries to measure really work in similar way between the populations of interest.[30]

Since the CAMPHOR is the first instrument specifically developed to evaluate HRQoL in PH, it has been the one most widely used in clinical studies, and there have been several publications describing in detail the process of culturally adapting it for use in different countries.[19-26] It is important to point out that, in the adapted versions, good psychometric properties, similar to those of the original version, were achieved.

The psychometric properties of the Spanish-language version of the CAMPHOR developed for use in Colombia were evaluated in a non-probabilistic sample of 81

Table 3. Cronbach's alpha coefficients.

CAMPHOR scale	Time point 1
Symptoms	0.89
Functioning	0.90
Quality of life	0.92

CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review.

Table 4. Test-retest reliability.

Test-retest reliability	CAMPHOR		
	Symptoms (n = 50)	Functioning (n = 51)	Quality of life (n = 51)
Correlation coefficient	0.79	0.79	0.84

Table 5. Coefficients of correlation between the Cambridge Pulmonary Hypertension Outcome Review and the Medical Outcomes Study 36-Item Short Form Healthy Survey, version 2.*

SF-36v2	CAMPHOR		
	Symptoms	Functioning	Quality of life
Physical functioning	−0.76	−0.76	−0.56
Role-physical	−0.73	−0.72	−0.74
Bodily pain	−0.57	−0.50	−0.62
General health	−0.67	−0.55	−0.55
Vitality	−0.77	−0.53	−0.67
Social functioning	−0.66	−0.48	−0.74
Role-emotional	−0.55	−0.34	−0.59
Mental health	−0.61	−0.39	−0.69

CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; and SF-36v2: Medical Outcomes Study 36 Item Short Form Healthy Survey, version 2. *All correlations were significant ($p < 0.01$).

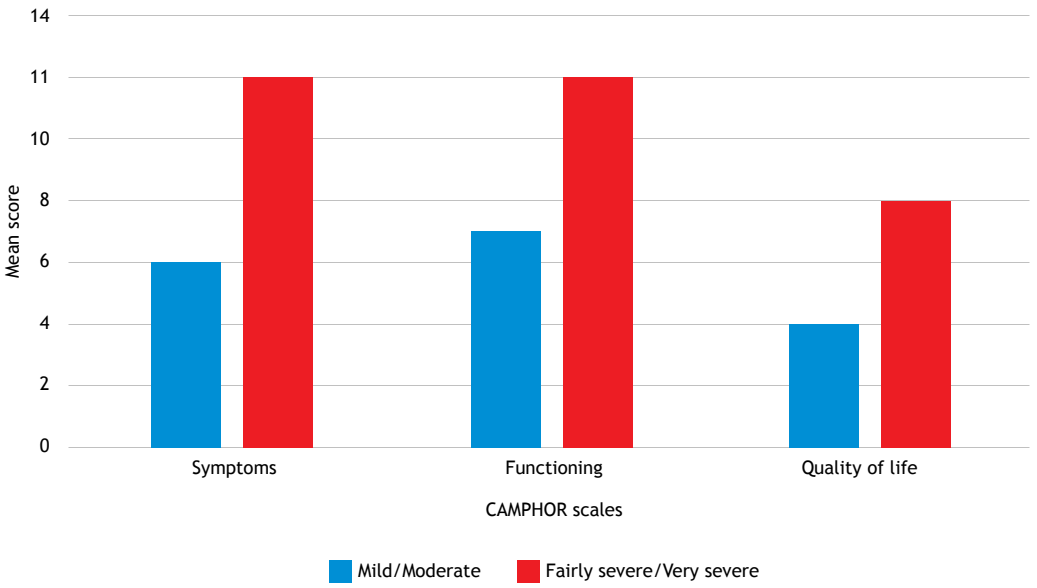

Figure 1. Mean Cambridge Pulmonary Hypertension Outcome Review scale scores by perceived disease severity. $p < 0.001$ for all.

subjects with PAH or CTEPH of different severities. The demographic characteristics of our population are similar to those of the population involved in the study that developed the original CAMPHOR and those of the populations involved in the different studies that culturally adapted and validated the CAMPHOR for use in other countries.[19-26]

The Cronbach's alpha coefficients for the symptoms, functioning, and quality of life scales at T1 and T2 were above the minimum required value of 0.70 (strong correlation), being considered appropriate and similar to those found for the original English-language version,[18] which confirms the good internal consistency of the Spanish-language version of the CAMPHOR developed for use in Colombia.

The percentage of patients scoring the minimum and maximum possible scores on this Spanish-language version of the CAMPHOR developed for use in Colombia was small, which means that the measurement of health status in patients with PAH or CTEPH is appropriate and supports the use of the instrument for post-intervention evaluation of changes.

The evaluation of convergent validity allows us to estimate the association between two constructs that are theoretically related to one another. In this study, the scales of the Spanish-language version of the CAMPHOR developed for use in Colombia were correlated with those of the SF-36v2. The CAMPHOR symptoms and functioning scales were found to have a strong correlation with the SF-36v2 physical functioning scale (0.76 for both) and role-physical scale (0.72 for both). The quality of life scale of the Spanish-language version of the CAMPHOR developed for use in Colombia showed strong correlations with the SF-36v2 role-physical and social functioning scales (0.74 for both), confirming that the two aspects are both affected by the disease and are associated with deterioration in quality of life.

The tool was able to discriminate between patients with mild/moderate disease and those with severe/very severe disease, with sicker patients scoring higher, which provides evidence of known group validity.

There are some potential limitations to our study. Although the participating subjects were recruited from specialized centers, they may not be necessarily representative of the general population in Colombia because of the sampling type, which may introduce a sampling bias. However, the bulk of patients diagnosed with PH are not usually managed in general hospitals or private practices, but rather in centers similar to ours, which are considered expert or "referral" centers for the management of the disease, and, therefore, the participating subjects could be considered representative.

Only clinically stable patients being treated on an outpatient basis were invited to participate in this study, and those who had very severe disease, were clinically unstable, and were hospitalized were excluded. Given that the study was not intended to evaluate the impact of PAH or CTEPH on quality of life, but rather to conduct a cultural and semantic adaptation of the CAMPHOR, we do not consider that the exclusion of those subjects will have affected this process.

Prospective studies using the Spanish-language version of the CAMPHOR developed for use in Colombia are needed to determine the impact of the disease on quality of life in our population.

The findings of this study suggest that the Spanish-language version of the CAMPHOR developed for use in Colombia as a self-administered, easy-to-use instrument was the result of a translation and cultural adaptation process that allows us to consider it conceptually, semantically, and technically equivalent to the original version, having shown good psychometric properties in a sample of patients between 18 and 79 years of age. Therefore, it can be used in research and clinical practice to assess the impact of health interventions on the HRQoL of patients with PAH or CTEPH in Colombia.

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Respiratory muscle strength and lung function in the stages of Parkinson's disease

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ABSTRACT

Objective: To investigate parameters of lung function and respiratory muscle strength in different stages of Parkinson's disease (PD), as well as to determine their correlation with motor function and quality of life. **Methods:** This was a cross-sectional study conducted at a referral center for PD in the city of Recife, Brazil. Respiratory muscle strength and lung function, as well as their relationship with motor function and quality of life, were evaluated in patients with PD, stratified by the level of severity, and were compared with the data obtained for a control group. After confirming the normality of data distribution, we performed one-way ANOVA with a post hoc t-test. **Results:** The sample comprised 66 individuals, in two groups: PD (n = 49) and control (n = 17). All of the parameters investigated showed inverse correlations with PD severity, and there were significant differences among the levels of severity, as well as between the PD and control groups, in terms of the MIP, MEP, FVC, FEV_1, and $FEF_{25-75\%}$. The lung function parameters also showed moderate to weak inverse correlations with bradykinesia and rigidity. On a quality of life questionnaire, the total score and mobility domain score both presented a moderate inverse correlation with FVC, FEV_1, PEF, and MEP. **Conclusions:** Respiratory muscle strength and some lung function parameters are impaired from the early stages of PD onward, bradykinesia and rigidity being the cardinal signs that correlate most strongly with impairment of those parameters. Such alterations negatively affect the quality of life of patients with PD.

Keywords: Parkinson disease; Respiratory mechanics; Maximum respiratory pressures; Quality of life.

INTRODUCTION

Respiratory dysfunction is the leading cause of death among individuals with Parkinson's disease (PD) and can be caused by respiratory muscle stiffness and postural dysfunction, as well as changes in upper airway muscle activation and coordination.[1]

As the disease progresses, lung function decreases in most patients, thus increasing the severity of PD.[2,3] Reduced lung function has been attributed to muscle stiffness and postural changes (including hyperkyphosis), which limit chest expansion and result in reduced lung volumes and restrictive lung disease.[4]

Although pulmonary dysfunction is a common and potentially serious complication in PD patients, respiratory symptoms are rare. This might be due to the fact that patients with PD generally have a sedentary lifestyle; that is, they are unable to complete enough physical exertion to induce respiratory adaptations that might promote respiratory dysfunction.[5,6] Therefore, it is important to assess respiratory muscle strength and lung function, as well as their impact on motor function, in patients with PD in order to implement therapeutic interventions aimed at improving respiratory muscle strength, lung function, and quality of life.[7,8]

The objective of the present study was to investigate parameters of lung function and respiratory muscle strength in different stages of PD, as well as to determine their correlation with motor function and quality of life.

METHODS

This was a cross-sectional study conducted at the Federal University of Pernambuco *Hospital das Clínicas* Neurology Outpatient Clinic, located in the city of Recife, Brazil. The study was conducted under the auspices of the Pro-Parkinson Outreach Program, which is a referral program for patients with PD. The study was approved by the local research ethics committee (Protocol no. 49958315.2.0000.5208).

Patients routinely followed at the outpatient clinic were personally invited to participate in the study. The convenience sample consisted of patients clinically diagnosed with idiopathic PD in accordance with the Brazilian National Ministry of Health criteria[9] and healthy

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individuals. Participants were divided into two groups: PD and control.

The criteria for inclusion in the PD group were as follows: having been diagnosed with PD in accordance with the original Hoehn and Yahr (H&Y) scale[10] and having no cognitive impairment, as assessed by the Mini-Mental State Examination.[11,12] The exclusion criteria were as follows: being under 40 years of age; being over 80 years of age; having a history of lung disease; having undergone thoracic surgery; having undergone surgery (deep brain stimulation or stereotactic surgery) to treat PD symptoms; and failing to complete all of the tests. The control group comprised healthy adults in the 55- to 80-year age bracket. Smokers and former smokers were excluded from the study.

Respiratory muscle strength parameters (MIP and MEP) were assessed with a digital manometer (MVD 300; Globalmed, Porto Alegre, Brazil), in accordance with international guidelines,[13] being expressed in cmH_2O. Three maneuvers were performed for each test, the best of the three being selected for analysis. Predicted values and percent predicted values were calculated from the equations provided by Pessoa et al.[14]

Spirometry was performed with a portable spirometer (EasyOne; ndd Medical Technologies, Zurich, Switzerland), in accordance with international guidelines.[15] The following parameters were measured: FVC, FEV_1, FEV_1/FVC, $FEF_{25-75\%}$, and PEF. Results were expressed as absolute values, predicted values, and percent predicted values, in accordance with Pereira et al.[16]

Motor function was assessed with subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) while patients were in an "on" state (i.e., using levodopa). UPDRS-III consists of 14 items (items 18-31) that can be scored as 0-4 based on severity.[17] The UPDRS was developed in 1987[18] and is widely used in order to monitor disease progression and drug treatment efficacy. It assesses signs, symptoms, and certain activities by self-report and clinical observation. It consists of 42 items divided into four parts: I) mentation, behavior and mood; II) activities of daily living; III) motor examination; and IV) complications of therapy. Individual item scores range from 0 (normality) to 4 (disabling disease).[17,18] Each subscale can be administered separately; answers to UPDRS-III are clinically assessed by a health professional.

Quality of life was assessed with the 39-item Parkinson's Disease Questionnaire (PDQ-39), which was adapted for use in Brazil in 2005, at the University of Oxford Department of Public Health and Primary Care Health Services Research Unit (in Oxford, UK).[19] The PDQ-39 is divided into 8 domains, total scores ranging from 0 to 100. A lower score translates to a better perceived quality of life. The total score and mobility domain score were correlated with lung function and respiratory muscle strength parameters.

The Shapiro-Wilk test was used in order to ascertain the normality of datasets. One-way ANOVA and a post hoc t-test were used in order to compare the groups. Pearson's correlation coefficient was used in order to measure the relationship among functional variables, symptoms of PD, and quality of life, being expressed as r and $\%r^2$. Values of r = 0.10-0.39 (0-15%) indicated a weak correlation, values of r = 0.40-0.69 (15-50%) indicated a moderate correlation, and values of r = 0.70-1.00 (50-100%) indicated a strong correlation, in accordance with the classification proposed by Dancey and Reidy.[20] All statistical analyses were performed with the Predictive Analytics Software package for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA), values of $p < 0.05$ being considered significant.

RESULTS

A total of 89 individuals (70 PD patients and 19 controls) were recruited. Of those, 23 (21 PD patients and 2 controls) were excluded. Therefore, the final sample consisted of 66 individuals (49 PD patients and 17 controls; Figure 1). Because only 3 patients with H&Y stage 4 PD completed all of the tests, the PD group was subdivided as follows: patients with H&Y stage 1 PD (the H&Y1 group), patients with H&Y stage 2 PD (the H&Y2 group), and patients with H&Y stage 3/4 PD (the H&Y3/4 group; Table 1).

MIP and MEP were significantly and inversely correlated with PD severity, as well as being significantly lower in the PD group than in the control group (Table 2). Similarly, FEV_1, PEF, and $FEF_{25-75\%}$, as well as percent predicted FVC, FEV_1, PEF, and $FEF_{25-75\%}$, were significantly and inversely correlated with PD severity, as well as being significantly lower in the PD group than in the control group. The differences between the H&Y3/4 group and the remaining groups were all significant (Table 3).

Some of the lung function parameters were significantly correlated with bradykinesia and rigidity. Bradykinesia showed a statistically significant moderate inverse correlation with FEV_1 and significant but weak inverse correlations with FVC, PEF, and $FEF_{25-75\%}$. Rigidity showed significant but weak inverse correlations with FVC and PEF. With regard to motor function, UPDRS-III scores showed significant but weak inverse correlations with $FEF_{25-75\%}$, PEF, and MEP (Table 4).

Total PDQ-39 scores and PDQ-39 mobility domain scores showed significant moderate inverse correlations with FVC, FEV_1, PEF, and MEP (Table 5).

DISCUSSION

In the present study, maximal respiratory pressures decreased with the progression of PD, with significant differences between controls and patients with PD at all levels of disease severity. This finding demonstrates that maximum respiratory pressures are lower in patients with PD than in individuals without the disease, regardless of disease severity. Specific PD features might play a larger role in this process than do aging-related losses. In patients with PD, respiratory muscle

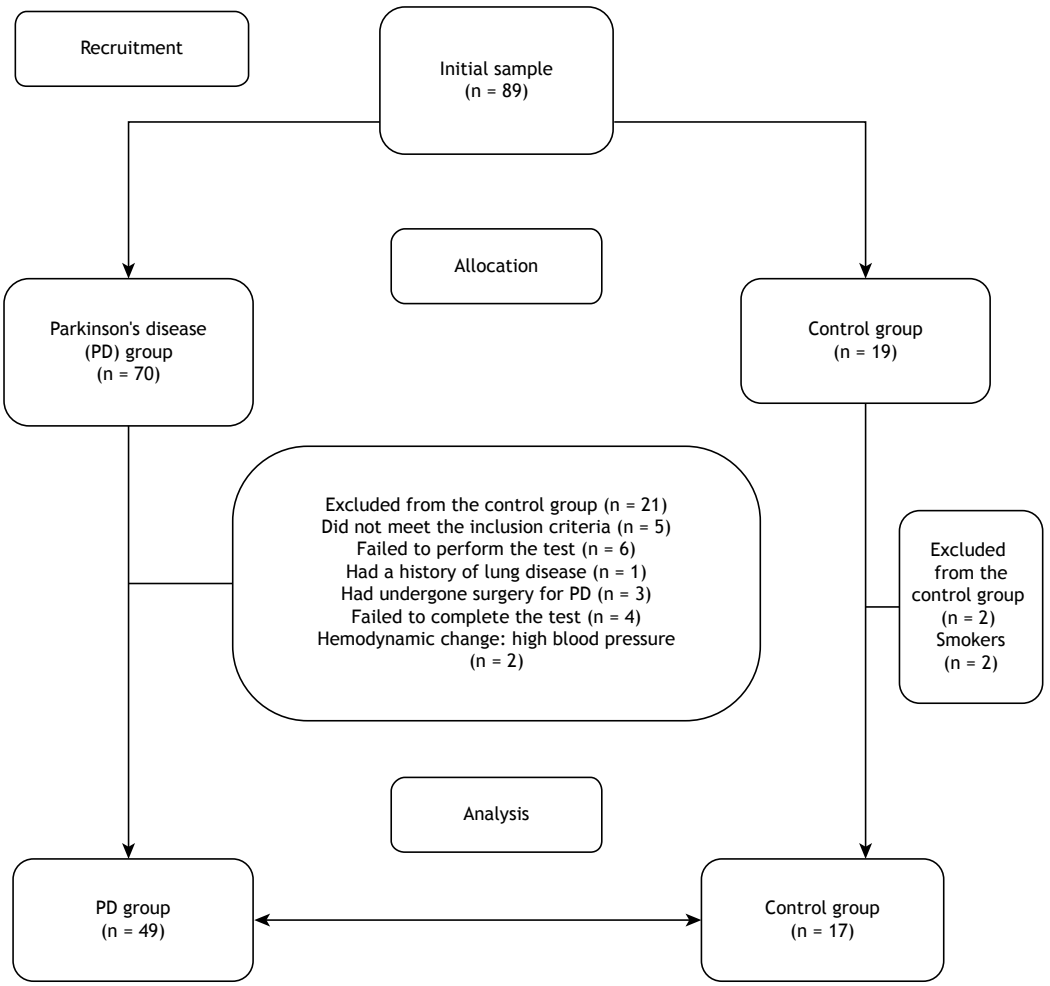

Figure 1. Flow chart of the data collection process.

weakness might be due to progressively reduced chest wall motion and, consequently, reduced tidal volume.[21] Therefore, reduced MIP and MEP values might be related to the inherent characteristics of PD, including postural changes (increased kyphosis), thoracic spine stiffness, and rib cage stiffness, all of which result in decreased muscle flexibility and control.[22,23] Chest muscle rigidity, bradykinesia, and tremors can severely compromise breathing in patients with PD.[22,24]

Parasympathetic hyperactivity results in impaired respiratory physiology and, consequently, airway smooth muscle constriction.[25] Patients with neuromuscular disease present with altered activity in the respiratory centers, as evidenced by impaired activation and coordination of the muscles that control central airway function.[26,27] Therefore, our findings are consistent with those of Seccombe et al.,[28] who found that MIP and MEP were below the normal range in 68% and 79% of patients, respectively. Sathyaprabha et al.[29] found that respiratory muscle strength was significantly lower in individuals with PD than in those without the disease. They found an improvement in MIP and MEP in PD patients receiving levodopa in comparison with those not receiving the drug. These findings are consistent with those of Weiner et al.[30]

In the present study, certain lung function parameters (FVC, FEV_1, $FEF_{25-75\%}$, and PEF) decreased significantly as PD progressed. Patients with PD typically present with restrictive lung disease, the most common changes being reduced tidal volume, reduced minute volume, and reduced inspiratory flow. These changes are related to respiratory muscle stiffness and hypokinesia, which are characteristic signs of PD.[6,28,29]

Although respiratory symptoms are rare in the early stages of PD, there have been reports of changes in lung function and respiratory mechanics in patients with PD.[18,26,29] Possible explanations for reduced lung volume and capacity include the following: impaired upper airway muscle function affecting airflow resistance and causing flow oscillation[27]; diaphragmatic flutter[30]; and reduced MEP.[31]

Significant inverse correlations were found between UPDRS-III scores and the following lung function parameters: FVC, FEV_1, PEF, and $FEF_{25-75\%}$. A worse motor function (i.e., a higher UPDRS-III score)

Table 1. Mean age, weight, height, and waist circumference, as well as their respective standard deviations, in controls and in patients at different stages of Parkinson's disease.

Variable	Controls	Parkinson's disease			p*
		H&Y1	H&Y2	H&Y3/4	
	N = 17 (100%)	n = 17 (35%)	n = 19 (39%)	n = 13 (26%)	
Age	66 (6)**	57 (9)**	63 (8)	67 (9)**	0.006**
Weight	68 (12)	70 (9)	73 (11)	73 (8)	0.53
Height	158 (6)	162 (8)	164 (10)	163 (6)	0.12
WC	99 (12)	91 (12)	97 (10)	96 (12)	0.24

H&Y: Hoehn and Yahr[10]; H&Y1: patients with H&Y stage 1 Parkinson's disease; H&Y2: patients with H&Y stage 2 Parkinson's disease; H&Y3/4: patients with H&Y stage 3/4 Parkinson's disease; and WC: waist circumference. *One-way ANOVA. **H&Y1 vs. controls and H&Y1 vs. H&Y3/4.

Table 2. Mean maximal inspiratory and expiratory pressures (in cmH_2O), as well as their corresponding standard deviations, in controls and in patients at different stages of Parkinson's disease.

Variable	Controls	Parkinson's disease			p*
		H&Y1	H&Y2	H&Y3/4	
	N = 17 (100%)	n = 17 (35%)	n = 19 (39%)	n = 13 (26%)	
MIP	−78.65 (22)	−59.00 (21)	−60.95 (20)	−48.85 (18)	0.001
Predicted MIP	70.04 (11)	80.97 (11)	80.65 (12)	79.76 (11)	0.02
MIP, % predicted	112 (27)	72 (19)	77 (25)	61 (18)	< 0.0001
MEP	106.53 (34)	85.76 (22)	90.00 (21)	73.69 (33)	0.016
Predicted MEP	103.02 (24)	112.64 (26)	115.30 (21)	111.19 (26)	0.29
MEP, % predicted	105 (28)	79 (22)	81 (25)	66 (26)	0.0005

H&Y: Hoehn & Yahr[10]; H&Y1: patients with H&Y stage 1 Parkinson's disease; H&Y2: patients with H&Y stage 2 Parkinson's disease; and H&Y3/4: patients with H&Y stage 3/4 Parkinson's disease. *One-way ANOVA and post hoc t-test (least significant difference). MIP: H&Y1 vs. controls ($p < 0.006$); H&Y2 vs. controls ($p < 0.011$); and H&Y3/4 vs. controls ($p < 0.001$). Predicted MIP: H&Y1 vs. controls ($p = 0.007$); H&Y2 vs. controls ($p = 0.007$); and H&Y3/4 vs. controls ($p = 0.02$). MIP, % predicted: H&Y1 vs. controls ($p < 0.0001$); H&Y2 vs. controls ($p < 0.0001$); and H&Y3/4 vs. controls ($p < 0.0001$). MEP: H&Y1 vs. controls ($p = 0.031$) and H&Y3/4 vs. controls ($p = 0.002$). MEP, % predicted: H&Y1 vs. controls ($p = 0.002$); H&Y2 vs. controls ($p = 0.003$); and H&Y3/4 vs. controls ($p < 0.001$).

Table 3. Mean lung function parameters and their corresponding standard deviations in controls and in patients at different stages of Parkinson's disease.

Variable	Controls	Parkinson's disease			p*
		H&Y1	H&Y2	H&Y3/4	
	N = 17 (100%)	n = 17 (35%)	n = 19 (39%)	n = 13 (26%)	
FVC, L	2.6 (0.6)	2.9 (0.6)	2.8 (1.0)	2.2 (0.9)	0.06
FVC, % predicted	88 (14)	85 (12)	79 (18)	61 (22)	0.0006
FEV_1, L	2.1 (0.5)	2.4 (0.5)	2.2 (0.7)	1.7 (0.7)	0.01
FEV_1, % predicted	90 (18)	84 (14)	79 (18)	59 (20)	0.0002
FEV_1/FVC	79.3 (4.5)	79.7 (5.3)	78.9 (6.9)	77.6 (4.3)	0.91
FEV_1/FVC, % predicted	100 (5)	100 (7)	100 (9)	990 (18)	0.97
PEF, L	5.0 (1.5)	6.0 (1.8)	4.8 (1.5)	3.2 (1.6)	0.0005
PEF, % predicted	68 (15)	72 (19)	56 (16)	36 (14)	0.0001
$FEF_{25-75\%}$	2.2 (0.8)	2.5 (0.7)	2.1 (0.7)	1.5 (0.9)	0.01
$FEF_{25-75\%}$, % predicted	98 (40)	98 (34)	84 (29)	61 (32)	0.01

H&Y: Hoehn & Yahr[10]; H&Y1: patients with H&Y stage 1 Parkinson's disease; H&Y2: patients with H&Y stage 2 Parkinson's disease; and H&Y3/4: patients with H&Y stage 3/4 Parkinson's disease. *One-way ANOVA and post hoc t-test (least significant difference). FVC, % predicted: H&Y1 vs. H&Y3/4 ($p < 0.001$); H&Y2 vs. H&Y3/4 ($p = 0.004$); and H&Y3/4 vs. controls ($p < 0.001$). FEV_1: H&Y1 vs. H&Y3/4 ($p = 0.002$) and H&Y2 vs. H&Y3/4 ($p = 0.012$). FEV_1, % predicted: H&Y1 vs. H&Y3/4 ($p < 0.001$); H&Y2 vs. H&Y3/4 ($p = 0.003$); H&Y2 vs. controls ($p = 0.05$); and H&Y3/4 vs. controls ($p < 0.001$). PEF: H&Y1 vs. H&Y2 ($p = 0.026$); H&Y1 vs. H&Y3/4 ($p < 0.001$); H&Y2 vs. H&Y3/4 ($p = 0.008$); and H&Y3/4 vs. controls ($p = 0.004$). PEF, % predicted: H&Y1 vs. H&Y2 ($p = 0.003$); H&Y1 vs. H&Y3/4 ($p < 0.001$); H&Y2 vs. H&Y3/4 ($p = 0.001$); H&Y2 vs. controls ($p = 0.003$); and H&Y3/4 vs. controls ($p < 0,001$). $FEF_{25-75\%}$: H&Y1 vs. H&Y3/4 ($p = 0.001$) and H&Y3/4 vs. controls ($p = 0.0043$). $FEF_{25-75\%}$, % predicted: H&Y1 vs. H&Y3/4 ($p = 0.003$) and H&Y3/4 vs. controls ($p = 0.003$).

translates to lower FVC, FEV_1, PEF, and $FEF_{25-75\%}$. The respiratory system of patients with PD is likely affected by impaired motor function, with reduced thoracic motion resulting in postural misalignment and osteoarticular degeneration, both of which affect respiratory mechanics.[32] Significantly increased motor symptoms, including bradykinesia and rigidity, which worsen when patients are off levodopa, have been

Table 4. Correlation of lung function and respiratory muscle strength parameters with cardinal signs and Unified Parkinson's Disease Rating Scale subscale III (motor examination) scores in patients with Parkinson's disease.

Variable	Cardinal signs, r (r^2, %)			Motor function, r (r^2, %)
	Tremor at rest	Rigidity	Bradykinesia	UPDRS III
FVC	0.05 (0.25)	−0.29 (8.4)*	−0.35 (12.2)*	−0.23 (5.2)
FEV_1	0.12 (1.4)	−0.27 (7.2)	−0.41 (16.8)*	−0.25 (6.2)
FEV_1/FVC	0.17 (2.8)	0.13 (1.6)	−0.10 (1.0)	-0.002 (0.0004)
PEF	−0.03 (0.09)	−0.35 (12.2)*	−0.37 (13.6)*	−0.31 (9.6)*
$FEF_{25-75\%}$	0.08 (0.64)	−0.25 (6.2)	−0.39 (15.2)*	−0.32 (10.2)*
MIP	−0.04 (0.14)	0.07 (0.4)	0.15 (2.25)	0.15 (2.2)
MEP	−0.03 (0.09)	−0.18 (3.2)	−0.25 (6.2)	−0.32 (10.2)*

UPDRS-III: subscale III of the Unified Parkinson's Disease Rating Scale. *Pearson's correlation; $p < 0.05$.

Table 5. Correlation of lung function and respiratory muscle strength parameters with quality-of-life questionnaire scores in patients with Parkinson's disease.

Variable	Quality of life	
	PDQ-39, r (r^2, %)	PDQ-39 mobility domain, r (r^2, %)
FVC	−0.39 (15.2)*	−0.38 (14.4)*
FEV_1	−0.36 (12.9)*	−0.36 (12.9)*
FEV_1/FVC	0.20 (4.0)	0.17 (2.8)
PEF	−0.31 (9.6)*	−0.30 (9)*
$FEF_{25-75\%}$	−0.19 (3.6)	−0.22 (4.8)
MIP	0.24 (5.7)	0.27 (7.2)
MEP	−0.42 (17.64)*	−0.37 (13.6)*

PDQ-39: 39-item Parkinson's Disease Questionnaire. *Pearson's correlation; $p < 0.05$.

shown to be associated with reduced lung function and impaired respiratory mechanics.[33,34] Our findings are consistent with those of a study in which a strong inverse correlation was found between PEF and PDQ-39 scores in patients with PD.[34]

With regard to quality of life, total PDQ-39 scores and PDQ-39 mobility domain scores showed moderate inverse correlations with FVC, FEV_1, PEF, and MEP. As the disease progresses, motor changes negatively affect patient physical, mental, emotional, and socioeconomic status, resulting in poor perceived quality of life. In addition, impaired mobility leads to social isolation and reduced activities of daily living, with progressive worsening of pulmonary complications.[35]

Although it is important to determine the impact that changes in lung function and respiratory mechanics have on the quality of life of patients with PD, few studies have addressed this issue, further studies therefore being required.

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Effects of a high-intensity pulmonary rehabilitation program on the minute ventilation/carbon dioxide output slope during exercise in a cohort of patients with COPD undergoing lung resection for non-small cell lung cancer

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ABSTRACT

Objective: Preoperative functional evaluation is central to optimizing the identification of patients with non-small cell lung cancer (NSCLC) who are candidates for surgery. The minute ventilation/carbon dioxide output (V_E/VCO_2) slope has proven to be a predictor of surgical complications and mortality. Pulmonary rehabilitation programs (PRPs) could influence short-term outcomes in patients with COPD undergoing lung resection. Our objective was to evaluate the effects of a PRP on the V_E/VCO_2 slope in a cohort of patients with COPD undergoing lung resection for NSCLC. **Methods:** We retrospectively evaluated 25 consecutive patients with COPD participating in a three-week high-intensity PRP prior to undergoing lung surgery for NSCLC, between December of 2015 and January of 2017. Patients underwent complete functional assessment, including spirometry, DLCO measurement, and cardiopulmonary exercise testing. **Results:** There were no significant differences between the mean pre- and post-PRP values (% of predicted) for FEV_1 (61.5 ± 22.0% vs. 62.0 ± 21.1%) and DLCO (67.2 ± 18.1% vs. 67.5 ± 13.2%). Conversely, there were significant improvements in the mean peak oxygen uptake (from 14.7 ± 2.5 to 18.2 ± 2.7 mL/kg per min; $p < 0.001$) and V_E/VCO_2 slope (from 32.0 ± 2.8 to 30.1 ± 4.0; $p < 0.01$). **Conclusions:** Our results indicate that a high-intensity PRP can improve ventilatory efficiency in patients with COPD undergoing lung resection for NSCLC. Further comprehensive prospective studies are required to corroborate these preliminary results.

Keywords: Carcinoma, non-small-cell lung; Pulmonary disease, chronic obstructive/rehabilitation; Carbon dioxide/metabolism; Oxygen consumption/physiology; Risk assessment.

INTRODUCTION

Risk stratification has always been considered crucial in patients with non-small cell lung cancer (NSCLC) undergoing lung resection. The decline in the respiratory function after surgery remains a noteworthy drawback despite the advances in surgical techniques and perioperative care. The current guidelines of the European Respiratory Society and the European Society of Thoracic Surgery[1] strongly suggest the assessment of patients' physical performance by a functional-based algorithm. Peak oxygen uptake (VO_{2peak}) has shown to be the best independent predictor of surgical complication rates[2-7] and, for this reason, cardiopulmonary exercise testing (CPET) is recommended when preoperative FEV_1 and/or DLCO are < 80% of the predicted values.[1] Therefore, preoperative evaluation of respiratory function is one of the most important factors to determine operability, especially in patients with COPD.[1-3,8] Although VO_{2peak} is certainly the most widely used variable, CPET provides various other direct and indirect indicators that change in response to incremental workloads. Consistent data are emerging about the relationship between minute ventilation (V_E) and carbon dioxide output (VCO_2), also called the ventilatory efficiency slope. Patients with lung disease have increased ventilatory requirements for a given level of exercise.[9] In two independent studies that involved patients undergoing lung resections, a higher V_E/VCO_2 slope showed to be a predictor of surgical complications and increased mortality.[3,8] A few studies reported the impact of preoperative pulmonary rehabilitation programs (PRPs) on exertional parameters in cohorts of NSCLC patients undergoing radical surgery.[10-12] Therefore, the

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aim of the present study was to evaluate the effects of a preoperative high-intensity PRP on the V_E/VCO_2 slope in a cohort of patients with COPD undergoing lung resection for NSCLC.

METHODS

Patients

We retrospectively evaluated the electronic medical records of 32 consecutive COPD patients attending a preoperative high-intensity PRP prior to undergoing lung surgery for NSCLC, between December of 2015 and January of 2017. Inclusion criteria were having been previously diagnosed with clinical stage I-IIIa NSCLC; being deemed fit for surgery according to the European Respiratory Society/European Society of Thoracic Surgery guidelines[1]; being < 80 years of age; having a body mass index of 18-34 kg/m^2; and presenting with a postbronchodilator fixed FEV_1/FVC ratio < 0.70. Exclusion criteria were contraindications to surgery based on baseline CPET; cardiovascular or musculoskeletal disorders limiting training; use of oxygen therapy or noninvasive ventilation for chronic lung failure; cognitive impairment or psychiatric disorders; and pregnancy. The PRP was offered to patients with COPD who had a VO_{2peak} ≤ 15.0 mL/kg per min or an FEV_1 ≤ 50% of the predicted value and were awaiting surgical resection. The inclusion of patients in the PRP was not a reason for postponing surgical resection in any case. Patients who were deemed fit for surgery underwent open thoracotomy or video-assisted lobectomy three weeks after the beginning of PRP. COPD treatment was not modified during the observation period. Complete functional assessment, including spirometry, DLCO measurement, and CPET, was carried out, in accordance with our routine practice, before and after the PRP, both prior to surgery.

CPET and evaluation of dyspnea

Before and after the PRP, CPET was performed using a ramp protocol and breath-by-breath measurements on a cycle ergometer (Ergoline Ergoselect; SensorMedics, Milan, Italy) connected to computerized analyzer (Vmax encore 29C; SensorMedics). Hemodynamic and respiratory parameters were monitored during the test, including blood pressure, SpO_2, heart rate (HR), electrocardiogram, exhaled O_2, and exhaled CO_2. The test started with a 2-min evaluation of the patient at rest, followed by a 2-min warm-up period during which the patient cycled freely. Exercise intensity was gradually increased based on the predicted workload for each patient. The test was interrupted when the patient reached the maximum predicted HR or whether other limitations occurred. At the end of the CPET, the reasons for exercise limitation and the perception of dyspnea, determined by the Borg scale, were registered.

PRP

A PRP, in daily 3-h sessions from Monday to Friday, was carried out for 3 consecutive weeks.[10] In brief, the program consisted of respiratory exercises on a bench, on a mattress pad, and using wall bars. Subsequently, high-intensity training for the upper limbs (on a rowing ergometer) and the lower limbs (on a treadmill or cycle ergometer) were carried out. For rowing and walking, training was conducted at a perceived exertion rating of 15-17 (hard to very hard) on the Borg Rating of Perceived Exertion scale.[13] For cycling, the exercise workload was set according to CPET results for each patient, starting with 70% of the maximum score reached in CPET and increased by 10 W when the patient was able to tolerate that workload for 30 min.[10,11] High-intensity exercises lasted for 10-15 min. In the presence of physical exhaustion or severe dyspnea, the exercise was prematurely interrupted. The training sessions were supervised by an experienced physical therapist.

Statistical analysis

Data are reported as frequencies, means, and standard deviations; for respiratory parameters, absolute and percentage of the predicted values were considered. Intragroup analysis was performed using a t-test for dependent variables. The level of significance was set at 5%.

RESULTS

Of the 32 patients evaluated, 7 were excluded because of incomplete PRP or lack of post-PRP assessment: 5 patients (15.6%) underwent surgery at other hospitals; and 2 (6.2%) abandoned the PRP after less than one week. Therefore, the sample comprised 25 patients (17 males and 8 females) diagnosed with resectable NSCLC (stage I-IIIa). The mean age was 62.3 ± 6.0 years. The baseline characteristics of the patients are summarized in Table 1, whereas Table 2 shows the comparison of characteristics between included and excluded patients. All of the patients had a baseline VO_{2peak} ranging from 10 to 20 mL/kg per min (mean, 14.7 ± 2.5 mL/kg per min). Three patients (12%) had a previous diagnosis of chronic heart failure, and 16 (64%) had systemic hypertension. Table 3 compares spirometry and CPET parameters before and after the 3-week PRP. As expected, the major spirometry variables showed no significant differences between the pre- and post–PRP values. Conversely, the VO_{2peak} improved significantly after the PRP (14.7 ± 2.5 mL/kg per min vs. 18.2 ± 2.7 mL/kg per min; $p < 0.001$), as did the V_E/VCO_2 slope (32.0 ± 2.8 vs. 30.1 ± 4.0; $p < 0.01$).

DISCUSSION

In the present study, we found that a high-intensity PRP in patients with COPD undergoing lung resection for NSCLC might influence exertional parameters by increasing VO_{2peak} and reducing the V_E/VCO_2 slope. The risk of lung cancer is approximately five times greater in patients with COPD than in smokers without COPD, regardless of age and smoking history.[14-18] In patients in the early stages of NSCLC,[19] the

Table 1. Baseline characteristics of the patients (N = 25).[a]

Characteristic	Result
Age, years	62.3 ± 6.0
Gender, male	17 (68)
Smoking history, pack-years	37.2 ± 8.0
BMI, kg/m^2	26.1 ± 3.4
FEV_1, L	1.67 ± 0.7
FEV_1, % predicted	61.5 ± 22.0
FEV_1/FVC	54.1 ± 13.1
TLC, % predicted	108.7 ± 28.6
IC, % predicted	84.4 ± 14.3
IC/TLC	38.5 ± 12.1
RV, % predicted	130.0 ± 39.4
DLCO, % predicted	67.2 ± 18.1
VO_{2peak}, mL/kg per min	14.7 ± 2.5
VO_{2peak}, % predicted	64.1 ± 19.2
COPD staging	
I	4 (16)
II	9 (36)
III/IV	12 (48)
COPD treatment	
LAMA	3 (12)
LABA	1 (4)
LABA/LAMA	16 (64)
LABA/LAMA/ICS	5 (20)
TNM staging	
Ia	6 (24)
Ib	8 (32)
IIa	7 (28)
IIb	4 (16)

BMI: body mass index; IC: inspiratory capacity; VO_{2peak}: peak oxygen uptake; LABA: long-acting β_2 agonists; LAMA: long-acting muscarinic antagonists, ICS: inhaled corticosteroids; and TNM: tumor-lymph node-metastasis. [a]Values expressed as n (%) or mean ± SD.

presence of coexisting COPD has been correlated with shorter survival, although no convincing evidence of such a correlation has been found in patients with nonresectable tumors.[20] In our study population, most of the subjects were heavy smokers with poor pulmonary function test results, which did not improve significantly after the high-intensity PRP. These data are consistent with those of similar studies in the literature[21,22] and could have been due to the short duration of the PRP. Nevertheless, exertional parameters improved meaningfully, indicating the positive effects of such a program on overall fitness and efficiency of CO_2 elimination. A previous prospective study[10] showed that VO_{2peak} could be influenced by a PRP. To our knowledge, there are as yet no data about the V_E/VCO_2 slope in relation to a PRP. The V_E/VCO_2 slope reflects a combination of factors that underlie ventilatory inefficiency and can be altered by both pulmonary and cardiac diseases. However, Corrà et al.[23] reported that a V_E/VCO_2 > 35 is a predictor of mortality, independently from VO_{2max}, in a cohort of patients with chronic heart failure. Those results were subsequently corroborated in three large studies that involved patients undergoing lung resection for NSCLC.[3,5,8] A comprehensive retrospective analysis investigated 145 consecutive patients with COPD referred for preoperative evaluation.[8] The authors concluded that a high V_E/VCO_2 slope can be considered an independent predictor of postoperative mortality among patients with COPD undergoing lung resection, no deaths having occurred in patients with a V_E/VCO_2 slope within the normal range.[8] Brunelli et al.[3] found that the V_E/VCO_2 slope was the only significant factor associated with the risk of complications, showing that the incidence of complications and mortality were 3- and 12-fold higher, respectively, among patients with a V_E/VCO_2 slope > 35 than among those with lower values. More recently, a V_E/VCO_2 slope > 35 (at maximal exercise) was strongly associated with the probability of mortality and postoperative complications, as well as with a 1-year survival rate of 40%.[5] However, the latter study had one major weakness: the authors did not clearly state whether mortality was related to cancer or not. The clinical meaning of those findings remains to be determined, not only in the context of postoperative pulmonary complications/mortality after lung resection due to lung cancer but also in the context of the clinical implications of excessive ventilation during exercise on exertional dyspnea in COPD. In fact, a decrease in the V_E/VCO_2 slope after a PRP could be influenced by increased CO_2 elimination and by reduced exercise ventilation after training. [24] Porszasz et al.[25] investigated the magnitude of improvement in exercise tolerance and dynamic hyperinflation in a population of severe COPD patients undergoing a 7-week high-intensity PRP. After the PRP, the patients showed decreased dynamic hyperinflation and breathing frequency during a constant work rate test on a cycle ergometer. In addition, the multivariate analysis revealed that the improvement in inspiratory capacity was significantly associated with the changes in exercise tolerance. However, the role of PRPs in the setting of NSCLC surgery has yet to be clarified. Mainini et al.,[26] in an elegant systematic review, emphasized that PRPs should be better studied due to the scarcity of randomized clinical trials regarding preoperative and postoperative PRPs, the few such studies having produced inconsistent results. The effects of pulmonary rehabilitation in COPD patients undergoing NSCLC surgery are currently under investigation in two clinical trials (NCT00363428 and NCT02887521). The effects of a longer PRP, including preoperative and postoperative training, are also under investigation (NCT02405273).

Despite the small number of patients, our study offers novel insights in this field of research. However, the present study has some limitations. First, because of the retrospective design of the study, we were unable to report the 1-year survival rate of the patients studied, which would be an interesting long-term outcome measure of the value of a PRP. In addition, the number of patients who were unable to complete

Table 2. Spirometry and cardiopulmonary exercise test parameters before and after the three-week pulmonary rehabilitation program.

Parameter	Before	After	p
FEV_1, % predicted	61.5 ± 22.0	61,9 ± 21.1	ns
VC, % predicted	81.1 ± 19.0	82.0 ± 17.8	ns
FEV_1/VC	54.1 ± 13.1	54.5 ± 14.1	ns
DLCO, % predicted	67.2 ± 18.1	67.5 ± 13.2	ns
VO_{2peak}, mL/kg per min	14.7 ± 2.5	18.2 ± 2.7	< 0,001
VO_{2peak}, % predicted	64.0 ± 19.2	81.1 ± 18.0	< 0,001
V_E/VCO_2 slope	32.0 ± 2.8	30.1 ± 4.0	< 0,01
Peak HR, % predicted	92.1 ± 1.8	92.3 ± 2.0	ns
Peak RER	1.2 ± 0.3	1.3 ± 0.2	ns
Breathing reserve, %	24.3 ± 6.1	24.7 ± 6.4	ns

ns: not significant; VO_{2peak}: peak oxygen uptake; V_E: minute ventilation; VCO_2: carbon dioxide output; and RER: respiratory exchange ratio.

Table 3. Baseline characteristics of included and excluded patients.[a]

Characteristic	Included patients	Excluded patients	p
Age, years	62.3 ± 6.0	60.4 ± 5.1	0.45
Gender			
Male	17 (68.0)	5 (71.4)	0.94
Female	8 (32.0)	2 (28.6)	0.90
Smoking history, pack-years	37.2 ± 8.0	32.2 ± 9.1	0.16
BMI, kg/m^2	26.1 ± 3.4	27.5 ± 2.9	0.33
FEV_1, L	1.67 ± 0.70	1.84 ± 0.60	0.56
FEV_1, % predicted	61.5 ± 22.0	63.4 ± 26.2	0.84
FEV_1/FVC	54.1 ± 13.1	59.1 ± 10.1	0.36
TLC, % predicted	108.7 ± 28.6	111.1 ± 27.2	0.83
IC, % predicted	84.4 ± 14.3	87.1 ± 12.9	0.64
IC/TLC	38.5 ± 12.1	35.4 ± 15.9	0.64
RV, % predicted	130.0 ± 39.4	124.5 ± 42.1	0.76
DLCO, % predicted	67.2 ± 18.1	71.0 ± 16.5	0.60
VO_{2peak}, mL/kg per min	14.7 ± 2.5	15.1 ± 2.8	0.73
VO_{2peak}, % predicted	64.1 ± 19.2	67.8 ± 21.1	0.68
COPD staging			
I/II	13 (52.0)	3 (42.8)	0.80
III/IV	12 (48.0)	4 (57.2)	0.81
TNM staging			
Ia-b	14 (56.0)	4 (57.1)	0.98
IIa-b	11 (44.0)	3 (42.9)	0.97

BMI: body mass index; IC: inspiratory capacity; VO_{2peak}: peak oxygen uptake; and TNM: tumor-lymph node-metastasis. [a]Values expressed as n (%) or mean ± SD.

the PRP and were therefore excluded from the final analysis represents a potential limitation of the study. However, no differences were found between the two groups at baseline.

In conclusion, our results underscore the influence of a high-intensity PRP on ventilation efficiency. Further comprehensive prospective studies are required in order to corroborate these preliminary results.

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Mortality and costs of pneumococcal pneumonia in adults: a cross-sectional study

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ABSTRACT

Objective: Pneumococcal pneumonia is a significant cause of morbidity and mortality among adults. The study's main aim was to evaluate the in-hospital mortality and related costs of community-acquired pneumococcal pneumonia in adults. **Methods:** This cross-sectional study used medical records of adult patients with pneumococcal pneumonia hospitalized in a university hospital in Brazil from October 2009 to April 2017. All patients aged ≥ 18 years diagnosed with pneumococcal pneumonia were included. Risk factors, intensive care unit admission, length of hospital stay, in-hospital mortality, and direct and indirect costs were analyzed. **Results:** In total, 186 patients were selected. The mean in-hospital mortality rate was 18% for adults aged < 65 years and 23% for the elderly (≥ 65 years). Bacteremic pneumococcal pneumonia affected 20% of patients in both groups, mainly through chronic respiratory disease (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01). Over 7 years, annual total direct and indirect costs were USD 28,188 for adults < 65 years (USD 1,746 per capita) and USD 16,350 for the elderly (USD 2,119 per capita). **Conclusion:** Pneumococcal pneumonia remains an important cause of morbidity and mortality among adults, significantly affecting direct and indirect costs. These results suggest the need for prevention strategies for all adults, especially for patients with chronic respiratory diseases.

Keywords: Pneumococcus; Pneumococcal disease; Pneumonia; Hospital costs; Mortality.

INTRODUCTION

Pneumococcal infection is a significant cause of morbidity and mortality worldwide. *Streptococcus pneumoniae*, or pneumococcus, is the main etiologic agent of community-acquired pneumonia (CAP) in children and adults.[1,2] Elderly people, patients with chronic conditions (chronic obstructive pulmonary disease, bronchial asthma, chronic cardiovascular disease, cerebrovascular disease, chronic renal disease, chronic liver disease, or diabetes mellitus), and immunosuppressed persons are at risk for pneumococcal pneumonia (PP) and bacteremic pneumococcal pneumonia (BPP).[3-7]

Ruiz et al. carried out a study published in 2017 comparing adults aged 18–64 years and elderly people (aged ≥ 65 years) who were diagnosed with PP. The authors found that patients aged ≥ 65 years had a higher 30-day mortality rate; however, elderly patients were less frequently admitted to intensive care units (ICUs) and had shorter hospital stays.[8] Epidemiological data from Europe revealed 21,118 confirmed cases of pneumococcal disease in 2015, with a mortality rate of 14% (1,312 patients) and hospital costs for PP and BPP of approximately 13,611 euros (EUR) per hospitalized patient.[9]

Hospitalizations of patients aged over 50 years have a greater economic impact, compared with hospitalizations of individuals aged 18 years or younger (average cost per episode of EUR 5,000 vs. EUR 2,750, respectively).[10,11] These rates of mortality and costs are higher in developing countries, and published data on PP in adults and its impact on health systems in these contexts are scarce.[11] The present study adds to the literature on the in-hospital mortality from PP and related direct and indirect costs, comparing elderly and younger adult patients in a university hospital in Brazil.

METHODS

Study design and population

This cross-sectional study used the medical records of adult patients diagnosed with PP hospitalized at the Hospital Geral de Caxias do Sul, Brazil. The study period spanned from October 2009 to April 2017, and all patients aged ≥ 18 years diagnosed with PP or BPP were enrolled. Ethical approval for analysis of the hospital records was obtained from the University of Caxias do Sul Research Ethics Committee (2.360.724).

Clinical and microbiological diagnosis of PP and BPP

CAP was diagnosed based on radiographic findings (new infiltrates compatible with a diagnosis of pneumonia on chest x-ray, tomography, or magnetic resonance imaging) and clinical findings (acute-onset clinical symptoms suggestive of a lower respiratory tract infection, such as cough, sputum production, fever, pleural chest pain, or dyspnea).

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Microscopy and phenotypic tests were used to identify *Streptococcus pneumoniae*.[12] PP was defined as at least one positive result for *S. pneumoniae* in sputum, tracheal bronchial aspirate, and/or bronchoalveolar lavage (BAL) associated with clinical and radiographic features of CAP. Sputum specimens with < 10 squamous epithelial cells, > 25 polymorphonuclear cells per low-power field (magnification, ×100) and predominant presence of Gram-positive diplococci were considered of sufficient quality for diagnosis. Semi-quantitative cultures of > 10^5 colony/mL for tracheal aspiration specimens and > 10^4 colony/mL for BAL samples were considered significant for PP. BPP was diagnosed based on isolating *S. pneumoniae* from blood cultures obtained before the parenteral administration of antibiotics in a patient with CAP.

Variables analyzed and covariates

The impact of mortality associated with PP among adults (aged < 65 years and aged ≥ 65 years) was evaluated by demographic (gender, age, occupation, and income) and clinical characteristics. Dependent patients were those who reported not having their own source of income (unemployed patients, students, and people living with relatives); low-income patients were those who declared monthly earnings of USD 1,190 or less; average-income patients were those who earned up to USD 2,975 monthly; and high-income patients were those who reported more than USD 2,975 in monthly income).[13] The following clinical covariates were analyzed: diagnosis of bacteremic and non-bacteremic pneumonia, admission and length of hospitalization for treatment in the ICU, total length of hospital stay, and related deaths, as well as the comorbidities of chronic cardiovascular disease (ischemic heart disease, coronary disease, heart failure, arrhythmia), chronic respiratory disease (chronic obstructive pulmonary disease, bronchial asthma), chronic liver disease (cirrhosis, chronic viral hepatitis), renal failure (acute kidney injury, chronic kidney disease), chronic neurological disease (stroke, dementia), immunosuppression (change in immunity caused by medication or disease other than acquired immunodeficiency syndrome), diabetes mellitus, smoking, human immunodeficiency virus (HIV, living with acquired immunodeficiency syndrome virus and CD4 ≤ 200 cells/mm^3) and alcohol abuse (daily alcohol intake of 80 g for men or 60 g for women, during at least the 12 months prior to inclusion in the study).[1,4,5]

Direct and indirect cost analysis

The cost per hospital stay was analyzed as the direct cost to the Brazilian Health System, defined by the length of hospital stay, medicines, laboratory and imaging exams, surgical procedures and bronchoscopy, daily ICU cost, medical costs, and other health care costs. Indirect costs were the patient's and/or caregiver's costs associated with absence from work and the related impact. The total cost was defined as follows: total cost = direct costs + indirect costs.[14]

Data on the direct per-patient cost of hospitalization were provided by the hospital's financial sector and were adjusted for the 2017 payment rate. Indirect costs were calculated considering the costs of the patient's and/or caregiver's productivity loss, multiplying the number of days by the average job salary, according to each profession declared at hospital admission. Dependent patients had a primary caregiver, with a longer follow-up period in the hospital, whose hours of work-related absence were considered in the indirect cost analysis. The mean national salary rate was obtained from the General Register of Employees and Unemployment of the Brazilian Ministry of Labor and Employment.[15] The amounts in Brazilian real (BRL) were converted into US dollars (USD) at the rate of 1 USD = BRL 3.18.

Statistical analysis

Statistical analyses were performed on the demographic and clinical variables, and the results are presented as frequencies and percentages, means and standard deviations, or medians and interquartile ranges. Patient characteristics were compared between the two groups (younger adults vs. elderly patients), as were variables related to PP, comorbidities, length of hospital stay, ICU admission, and outcomes. The Kaplan–Meier method was used to determine associations between age groups and survival. Chi-square tests or Fisher's exact tests were used for the comparison of qualitative variables, and Student's *t*-test was used for quantitative variables. Multivariate analyses are reported as odds ratios (ORs) and 95% confidence intervals (CIs), with the younger patients (age < 65 years) as the reference group. The statistical model was estimated using logistic regression with the backward Wald method. The final models were created to predict in-hospital death and pneumococcal bacteremia assessing the general performance of the models, that is, the variation in the predicted outcome explained by the model independent variables, using Cox and Snell R-squared values (adjusted R^2). *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using R software, version 3.3.3 for Windows.

RESULTS

In total, 186 patients with PP or BPP criteria were included in the study, and none had previously been vaccinated with any pneumococcal vaccine. Of these patients, 127 were adults aged 18 to 64 years, and 59 were elderly people aged 65 years or older. The mean age for adults aged < 65 years was 46 ± 11.5 years, and the mean age for the elderly group was 70 ± 4.8 years. Most elderly patients were dependent or low-income. Table 1 summarizes all patients' baseline characteristics, stratified by age.

Table 1. Characteristics of patients with pneumococcal pneumonia.

Characteristic	Age < 65 years (n = 127)	Age ≥ 65 years (n = 59)	P value
Male, n (%)	78 (62.4)	40 (67.8)	0.40
Age (in years), mean (SD)	46 (36-55)	70 (67-72)	0.001
Average income, n (%)			
Dependent	38 (30)	17 (29)	0.30
Low	80 (63)	42 (71)	
Average	9 (7)	0 (0)	
High	0 (0)	0 (0)	
Pneumonia, n (%)			
Pneumococcal pneumonia	102 (80)	48 (81)	0.86
Bacteremic pneumococcal pneumonia	25 (20)	11 (19)	
Comorbidities, n (%)			
Chronic heart disease	36 (28.3)	31 (52.5)	< 0.01
Chronic respiratory disease	47 (37.0)	35 (59.3)	< 0.01
Chronic liver disease	11 (8.6)	0 (0)	< 0.01
Chronic renal disease	11 (8.6)	3 (5.0)	< 0.01
HIV	29 (22.8)	0 (0)	< 0.01
Chronic neurological disease	8 (6.3)	5 (8.5)	0.60
Immunosuppression	19 (14.9)	17 (28.8)	0.02
Diabetes mellitus	6 (4.7)	4 (6.7)	0.50
Smoking	46 (36.2)	24 (40.6)	0.60
Alcohol abuse	25 (19.7)	10 (16.9)	0.60
ICU admission, n (%)	33 (25.6)	17 (28.8)	0.10
Mean length of stay (days)			
Total	10 (7-15)	14 (5-22)	0.46
ICU	3 (0-5)	2 (0-3)	0.40
Death, n (%)	23 (18.1)	14 (23.7)	0.34

SD: standard deviation, HIV: human immunodeficiency virus, ICU: intensive care unit.

The institutional antimicrobial treatment protocol for CAP was based on the Brazilian Thoracic Association guideline, obtaining full compliance by verification of the Infection Control Service. All clinical cases are discussed on a daily basis with this team, both in intensive care units, as well as in the clinical and emergency departments. The empirical hospital therapy for CAP, adjusted for local epidemiology, includes the use of penicillins with beta-lactamase inhibitors or third generation cephalosporins, with or without macrolide association, depending on the severity of the patient. All strains of pneumococcus isolated from both respiratory tract and blood cultures were sensitive to penicillins, cephalosporins, quinolones and vancomycin. However, 12% resistance to erythromycin and 33% resistance to sulfamethoxazole/trimethoprim were observed in respiratory tract strains. Thus, the empiric antimicrobial treatment did not show impact on mortality in the different age groups of the study population due to the low rate of bacterial resistance to the standard treatment for PP and BPP.

BPP affected 20% of the selected patients, with no difference between the two age groups (p = 0.86). Comorbidities such as chronic heart disease, chronic respiratory disease, and immunosuppression were more prevalent in the elderly population (p < 0.01), whereas chronic liver disease, chronic renal disease, and HIV infection were more frequently observed in the younger adult population (p < 0.01). Chronic neurological disease, diabetes mellitus, smoking, and alcohol abuse did not differ significantly between the two age groups.

A total of 25.6% patients younger than 65 years and 28.8% of the elderly patients were admitted to the ICU with a mean length of stay of 3 days for both groups. The mean total length of hospital stay was 10 days for younger adults and 14 days for the elderly. During the study period, 37 patients died (19.9%), accounting for 18.1% of the younger adults and 23.7% of the elderly patients. The Kaplan–Meier curve presented in Figure 1 shows the patients' survival curve according to age and length of hospital stay. Both groups had similar results until the 20th day of hospitalization, after which there was a decrease in the survival of the elderly patients.

Regarding the risk of in-hospital death because of PP, ICU admission was associated with a higher mortality rate (OR: 156.3, 95% CI: 34.1–715.9, p < 0.001), with no difference in mortality between the two age groups

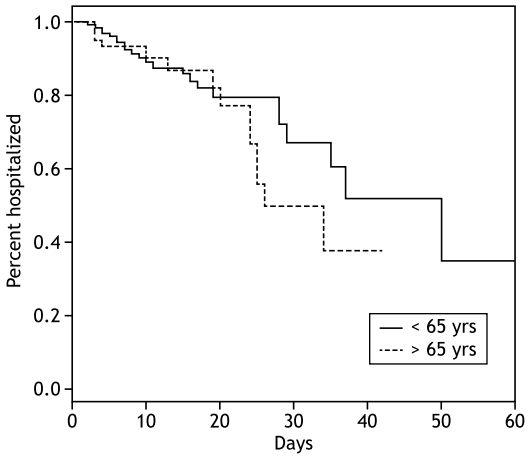

Figure 1. Kaplan-Meier curve on hospital survival analysis of adult (<65 years) and elderly (≥ 65 years) patients with pneumococcal pneumonia.

(OR: 1.41, 95% CI: 0.66–2.98, p = 0.40), as shown in Table 2. Of the comorbidities evaluated for BPP, in both age groups only chronic respiratory disease had an impact (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01) (Table 3).

The costs related to PP and BPP are described in Table 4. The average amount spent on direct and indirect costs annually was USD 28,188 for adult patients aged < 65 years and USD 16,350 for patients aged ≥ 65 years. During the 7-year study period, the total annual direct cost for PP was USD 24,458 for adults aged < 65 years and USD 14,676 for the elderly. The costs per hospitalized patient, considering both direct and indirect costs, were USD 1,746 for adults aged < 65 years and USD 2,119 for the elderly. The Brazilian Ministry of Health spent USD 1,515 on direct costs for each hospitalized adult aged < 65 years with PP and USD 1,902 on direct costs per patient aged ≥ 65 years.

Table 2. Multivariate logistic regression analysis predicting hospital mortality associated with pneumococcal pneumonia.

Risk factor	OR	95% CI	P value
Aged ≥ 65 years	1.41	0.66-2.98	0.40
Chronic respiratory disease	0.40	0.18-0.88	0.02
Chronic heart disease	1.10	0.52-2.32	0.80
Chronic liver disease	1.56	0.39-6.20	0.50
Chronic renal disease	2.43	0.76-7.74	0.15
HIV	0.60	0.20-1.85	0.35
Chronic neurological disease	1.89	0.55-6.50	0.31
Immunosuppression	0.97	0.39-2.52	0.94
Smoking	1.17	0.56-2.43	0.70
Alcohol abuse	1.52	0.60-3.60	0.35
Diabetes mellitus	0.43	0.05-3.52	0.40
Bacteremic pneumonia	0.57	0.25-1.32	0.20
ICU mortality	156.3	34.1-715.9	< 0.001

HIV: human immunodeficiency virus, ICU: intensive care unit, OR: odds ratio, CI: confidence interval.

Table 3. Multivariate logistic regression analysis predicting risk factors associated with bacteremic pneumococcal pneumonia.

Risk factor	Adjusted OR	95% CI	P value
Aged ≥ 65 years	0.77	0.32-1.90	0.58
Chronic respiratory disease	3.07	1.23-7.65	0.01
Chronic heart disease	0.88	0.36-2.16	0.77
Chronic liver disease	0.76	0.16-3.23	0.68
HIV	1.16	0.37-3.64	0.80
Chronic neurological disease	1.87	0.35-9.89	0.43
Immunosuppression	2.55	0.80-8.18	0.09
Diabetes mellitus	0.60	0.13-2.81	0.53

HIV: human immunodeficiency virus, OR: odds ratio, CI: confidence intervals.

Table 4. Costs related to hospitalization for pneumococcal pneumonia.

Costs	Aged < 65 years	Aged ≥ 65 years
Direct costs per capita	USD 1,515	USD 1,902
Indirect costs per capita	USD 231	USD 216
Total cost per capita	USD 1,746	USD 2,119
Total annual cost	USD 28,188	USD 16,350

USD: United States dollar.

DISCUSSION

Pneumococcal disease has a high incidence among adults aged < 65 years and among the elderly, contributing significant direct and indirect costs to the public health system. Although PP mainly affects patients with comorbidities, there was no observed difference in mortality between patients aged < 65 years and those aged ≥ 65 years. Patients with chronic respiratory diseases were at higher risk for bacteremic pneumonia, but these patients' mortality risk was not higher, compared with patients without this comorbidity.

Our study population was stratified into a younger adult group (aged 18 to 64 years) and an elderly group (aged ≥ 65 years). We found no statistical difference for in-hospital mortality between the two groups, demonstrating the significance of this disease for adult patients of all ages. In a study conducted in 2017, elderly patients had a higher 30-day mortality (OR: 6.83; 95% CI: 1.22–38.22; p = 0.028) than younger adults. This outcome may be related to immunosenescence because the participants were healthy and functional elderly people.[8]

The presence of chronic diseases influences both the chance of acquiring PP because of changes in immune response and the severity of the disease and its outcomes. Patients with comorbidities have a high rate of pneumococcal disease-related mortality in short- (30 days) and long-term (1 year) periods. The comorbidities associated with PP are chronic heart, respiratory, and liver diseases; acute or chronic renal failure; immunosuppression; chronic neurological diseases (among institutionalized patients); HIV; diabetes mellitus; smoking; and alcohol abuse.[16,17]

In the present study, heart disease occurred in 52.5% of elderly patients (p < 0.01) and did not have an impact on mortality in either age group (OR: 1.1, 95% CI: 0.52–2.32, p = 0.8). Musher et al. demonstrated that 19.4% of patients admitted to the hospital with PP had more than one cardiac event during the hospitalization.[18] According to Corrales-Medina et al., patients with heart disease account for a quarter of patients with CAP and have a 60% risk of 30-day mortality, especially in cases of heart failure (OR: 4.3), arrhythmia (OR: 1.8), or coronary disease (OR: 1.5).[19]

Torres et al., in their review of risk factors for pneumococcal disease, showed that chronic lung disease was an independent risk factor for pneumococcal CAP, especially in the elderly.[16] Chronic obstructive pulmonary disease and bronchial asthma were the most prevalent comorbidities found in both age groups of our studied population, with increased risk for bacteremic pneumonia (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01). Patients with chronic obstructive pulmonary disease have lung architectural changes that predispose them to respiratory infections, and adults with asthma have a 12% to 17% attributable risk of acquiring invasive pneumococcal infections, especially if there are frequent asthma exacerbations.[20,21]

Pneumococcal disease has previously been identified as a significant cause of morbidity in cirrhotic patients. However, in our study only 11 patients aged < 65 years had liver disease, with no impact of this condition on mortality (OR: 1.56: 95% CI: 0.39–6.20, p = 0.5). A study published in 2011 showed that cirrhotic patients had a higher risk for CAP (46.3% vs. 33%, p = 0.007).[22] In a Spanish study, patients aged 18–64 years with liver disease had a higher index of hospitalization for PP (OR: 56.3, 95% CI: 49.1–64.6) than patients aged ≥ 65 years (OR: 15.0, 95% CI: 13.1–17.2).[23]

Chronic renal disease is an important cause of mortality worldwide, and the incidence of pneumonia in dialysis patients is 27.9/100 persons/year, with a 1-year survival rate of 0.51.[24] In our study, chronic renal failure was more prevalent in the population aged < 65 years (p < 0.01), but there was no impact of this condition on mortality (p = 0.15). Several studies have suggested a relationship between chronic renal disease and PP, although the pathophysiological mechanisms involved are not well understood.[25]

Several existing studies have suggested that a high risk of pneumococcal disease is associated with primary immunodeficiency due to B cell defects.[26] Solid tumors and hematological malignancies also predispose individuals to infections, especially by gram-positive bacteria.[27] In the studied population, immunosuppression was more prevalent in the elderly (p = 0.02).

HIV infection was also a relevant risk factor for PP (p < 0.01) in the younger adult group, with no impact in mortality or BPP. The risk of invasive pneumococcal disease has been shown to be elevated in patients living with HIV, especially those with CD4 < 200 cells/mm^3, even with the adequate use of antiretroviral therapy.[28,29]

Studies have evaluated the relationship between smoking and pneumococcal disease in adults. Chun et al. published a study in 2015 on the association between passive smoking and invasive pneumococcal disease in 171 children; they found no association with PP.[30] Nuorti et al. found that active smoking was a strong risk factor for invasive disease in immunocompetent adults (OR: 4.1, 95% CI: 2.4–7.3).[31] In another study published in 2017, smoking was associated with a decreased risk of mortality (OR 0.52, CI 0.31 – 0.87).[32] In our study, tobacco use had no impact on PP or BPP among the age groups evaluated.

Alcohol abuse has been linked to the independent risk of acquiring CAP.[33] In a study of 19,000 subjects followed for 10 years, the overall mortality attributed to PP among alcohol users was 30%, compared with 17% among non-users of alcohol.[34] In our study, 25 (19.7%) adults aged < 65 years and 10 (16.9%) elderly patients were classified as suffering from alcohol abuse. We found no impact of alcohol abuse on mortality during hospital stay (p = 0.35). Chronic neurological diseases and diabetes mellitus also had no impact on mortality. Whereas chronic neurological diseases have a higher incidence in the elderly,

diabetes mellitus has been linked to PP in patients aged <40 years, with an increased risk for bacteremic pneumonia (ORs: 1.4 to 4.6).[16]

We observed BPP to affect 20% of the selected patients, with no difference between the age groups (p = 0.86), and there was no impact on the length of stay or in-hospital mortality. This incidence of BPP corresponds to previously published data showing that 25% to 30% of patients with PP had concomitant bacteremia and that approximately 75% of all pneumococcal diseases were non-bacteremic PP.[35] The length of hospital stay because of PP or BPP was higher for elderly patients (mean: 14 days), as was the rate of ICU admission (28.8% among the elderly vs. 25.6% among younger adults). A study conducted in the Netherlands in 2016 had similar results, with an average length of hospital stay of 12 days.[10] Ruiz et al. identified a mortality risk in the ICU of 4.2 (p = 0.10);[8] however, in our study, the in-hospital mortality was higher (OR: 156.3) because all 37 patients who died were in the ICU.

In terms of costs related to PP and BPP, the average amount spent annually on direct and indirect costs was higher in the population aged < 65 years (USD 28,188 for younger adults vs. USD 16,350 for the elderly) because of the number of adults in the younger age group enrolled and the related indirect costs of hospitalization of the economically active population. In the per capita analysis, however, the cost was higher for the elderly population (USD 2,119 vs. USD 1,746 for adults aged < 65 years) because of the direct costs of prolonged hospitalization and the incidence of comorbidities. A European study showed the average direct costs of CAP treatment to be EUR 196 in the outpatient setting and EUR 1,553 in the hospital setting. A Japanese study demonstrated an average patient treatment cost of USD 4,851.[36,37]

The limitations of our study included the lack of data on 30-day outpatient mortality, on the association with mortality and pneumococcal serotypes, and on patients' influenza vaccine status. Data on outpatient follow up would be relevant to evaluate quality of life after hospital discharge, as well as the association of the serotype and impact of pneumococcal vaccination in this population. Despite the lack of data on influenza vaccination, no co-infection with the virus was diagnosed in the study population.

In conclusion, despite being a monocentric study, the results demonstrate an important cost impact and mortality among the analyzed adult population. The incidence of disease and mortality was similar in the two age groups studied, regardless of the comorbidities, with a slight increase of PP in the population that has chronic respiratory diseases. The economic impact affects both the public health system in direct costs, and the society through indirect costs. Therefore, preventive measures should be urgently encouraged in all age groups, and cost-effectiveness studies should be conducted to assess the possible impact of preventive strategies, such as the pneumococcal vaccine, for all the adult population.

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Diagnosis and treatment of latent tuberculosis infection in patients undergoing treatment with immunobiologic agents: a four-year experience in an endemic area

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ABSTRACT

Objective: To describe the incidence of active tuberculosis and the occurrence of adverse events after isoniazid treatment in patients with latent tuberculosis infection (LTBI) who also had chronic inflammatory diseases and were treated with immunobiologic agents in an endemic area in Brazil. **Methods:** The diagnosis of LTBI was based on anamnesis, clinical examination, chest X-ray, and a tuberculin skin test (TST). Patients received prophylactic treatment (isoniazid for six months) in accordance with the Brazilian guidelines. **Results:** A total of 101 patients were evaluated between July of 2011 and July of 2015. Of those, 55 (54.46%) were women (mean age, 53.16 ± 1.76 years) and 46 (45.54%) were men (mean age, 45.39 ± 2.13 years). A total of 79 patients (78.22%) were being treated with immunobiologic agents and 22 (21.78%) were being treated with immunomodulatory or immunosuppressive agents. In the screening for LTBI, 53 patients (52.48%) had a TST induration ≥ 10 mm. Chest X-ray findings consistent with LTBI were observed in 36 patients (35.64%). Isoniazid preventive therapy was effective in 96 (95.05%) of the 101 patients evaluated. It is of note that 84 (83.17%) of the patients experienced no adverse effects from the use of isoniazid and that 83 (98.81%) of those patients completed the prophylactic treatment (p = 0.002). Active tuberculosis was diagnosed in 5 (6.33%) of the 79 patients treated with immunobiologic agents and in 1 (4.55%) of the 22 patients treated with other immunomodulators/immunosuppressants. **Conclusions:** A six-month course of isoniazid proved to be safe and effective in the treatment of LTBI, which is essential to reducing the risk of developing active tuberculosis.

Keywords: Latent tuberculosis; Tuberculin test; Tumor necrosis factors/antagonists & inhibitors; Isoniazid.

INTRODUCTION

Tuberculosis is an airborne infectious disease caused by *Mycobacterium tuberculosis*; because tuberculosis incidence and mortality are high, surveillance and treatment are a priority according to the World Health Organization.[1]

Approximately 2 billion people worldwide are infected with *M. tuberculosis*, and approximately 1 in 10 individuals will develop tuberculosis at some point in their lives. Although mortality from tuberculosis has significantly decreased, the World Health Organization estimated that there were 10.4 million new cases of tuberculosis worldwide in 2016, i.e., 140 cases per 100,000 population.[2]

Brazil is one of the 22 countries that collectively account for 80% of all cases of tuberculosis worldwide, ranking 16th in terms of absolute numbers of cases (66,796 in 2016) and 22nd in terms of tuberculosis incidence rate (32.4/100,000 population in 2016).[3]

Some groups are more susceptible to tuberculosis infection than the general population, including people living with HIV/AIDS and patients with immune-mediated chronic inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, and Crohn's disease, as well as patients with immunosuppressive conditions such as diabetes, chronic kidney disease, and solid organ transplantation. Patients with chronic inflammatory diseases are currently treated with immunosuppressants or immunomodulators; they are increasingly being treated with anti-TNF biologic agents and are at an increased risk of developing opportunistic infections, including tuberculosis.[1,4]

TNF inhibitors revolutionized the clinical treatment of chronic inflammatory diseases, improving the quality of life of patients. However, biologic agents increase the risk of developing tuberculosis. TNF plays an essential role in maintaining the immune response, particularly the integrity of granulomas in tuberculosis infection. In addition, TNF directly activates macrophages, which are responsible for phagocytosis of pathogens. In nearly 90% of individuals infected with *M. tuberculosis*, the bacilli remain contained within granulomas, resulting in latent

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tuberculosis infection (LTBI). Approximately 5-10% will develop active tuberculosis disease, the risk being highest in the first 5 years following infection.[5]

Given that TNF-α is a mediator of inflammatory pathways and has bactericidal properties, the adverse consequences of TNF-α inhibition raise major concerns for treatment with biologic agents. TNF-α inhibitors can cause severe immunosuppression, which leads to failure to control LTBI and, consequently, tuberculosis disease, reinfection with *M. tuberculosis* having been reported in several studies of patients treated with biologic agents.[4]

The primary objective of the present study was to describe the incidence of active tuberculosis and the occurrence of adverse events after isoniazid treatment in patients with LTBI and chronic inflammatory disease treated with biologic agents in an endemic area in Brazil.

METHODS

This was a prospective cohort study involving 101 patients with immune-mediated chronic inflammatory diseases. All of the patients were candidates for treatment with biologic agents and tested positive for LTBI, isoniazid preventive therapy (IPT) therefore being indicated. The selected patients were followed for 4 years. The study was conducted at a university hospital between June of 2011 and June of 2015, being approved by the local research ethics committee (Protocol no. 058.05.11).

The diagnosis of LTBI was based on anamnesis, clinical examination, chest X-ray, and a Mantoux tuberculin skin test (TST), being made after active tuberculosis disease had been excluded. The TST was performed by a trained technician in the clinical analysis laboratory of the hospital and consisted of delivering PPD RT23 tuberculin intradermally in the middle third of the volar aspect of the left forearm at a dose of 0.1 mL, which is equivalent to two tuberculin units. The results of the TST were read 72 h after PPD RT23 administration. A TST induration ≥ 5 mm was considered positive. Posteroanterior and lateral chest X-rays were performed in the radiology department of the hospital and were evaluated by two independent physicians (a radiologist in the radiology department of the hospital and a pulmonologist). Chest X-ray findings were classified as normal, abnormal because of the presence of granuloma or a small calcified nodule, or abnormal because of the presence of other, minimal, residual changes (striae, nodular fibrosis, pleural thickening, or any combination of the three). The history of risk factors for tuberculosis, including respiratory symptoms, current or previous tuberculosis treatment, and a history of exposure to tuberculosis, was also evaluated.

IPT was performed in accordance with the Third Brazilian Thoracic Association Guidelines on Tuberculosis,[6] i.e., at a dose of 5-10 mg/kg of body weight (maximum dose, 300 mg/day) for 6 months. Treatment with biologic agents was initiated no sooner than 1 month after initiation of IPT. Adverse reactions to isoniazid and clinical outcomes of IPT were evaluated. Figure 1 shows a flow chart of LTBI screening outcomes among candidates for treatment with TNF-α inhibitors.

Isoniazid toxicity was measured during IPT by determining serum levels of alanine aminotransferase and aspartate aminotransferase. Hepatotoxicity was defined as elevated liver transaminase levels (≥ three- to fivefold above the upper limit of normal).[7]

All statistical analyses were performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). The two-tailed Pearson's chi-square test with Yates' correction was used in order to determine significant associations. The two-tailed Fisher's exact test was used for contingency tables with fewer than five cells ($p < 0.05$), and the Student's t-test was used in order to compare the means. A multivariate analysis was performed in order to assess the strength of association among variables of interest; ORs, prevalence ratios (relative risk), and their respective 95% CIs were calculated. Values of $p < 0.05$ were considered significant.

RESULTS

A total of 101 patients were included in the analysis. Of those, 55 (54.46%) were women (mean age, 53.16 ± 1.76 years) and 46 (45.54%) were men (mean age, 45.39 ± 2.13 years). Patient age ranged from 21 years to 76 years (Table 1). Of the 101 participants, 79 (78.22%) were being treated with biologic agents and 22 (21.78%) were being treated with immunomodulatory or immunosuppressive agents. Most (n = 84) of the patients (83.17%) had rheumatic diseases, including rheumatoid arthritis (in 42) and ankylosing spondylitis (in 42). Of the 55 women in the sample, 34 (61.82%) had rheumatoid arthritis. Of the 46 men, 31 (67.39%) had ankylosing spondylitis. In addition, 9 patients (7.92%) had psoriasis and 8 (8.91%) had Crohn's disease (Table 1). With regard to LTBI screening, 53 patients (52.48%) had a TST induration > 10 mm. TST induration ranged from 5 mm to 40 mm, with a mean TST induration of 12.06 ± 0.60 mm. The mean TST induration was 7.31 ± 0.28 mm in the patients with a TST induration of 5-10 mm and 16.36 ± 0.70 mm in those with a TST induration ≥ 10 mm (Table 1).

With regard to epidemiological risk factors, 39 patients (38.61%) reported a history of contact with a tuberculosis case. In addition, 10 (9.90%) reported having previously received tuberculosis treatment and 18 (17.82%) reported respiratory symptoms. Furthermore, 83 (82.18%) had been vaccinated with BCG. Moreover, 36 (35.64%) had chest X-ray findings consistent with LTBI (Table 1).

With regard to the number of patients receiving treatment with immunomodulators, immunosuppressants, or a combination of the two when the TST was performed, 46 (45.54%) were being treated with ≥ 10 mg of weekly methotrexate (mean weekly dose, 12.837 ± 0.614 mg) and 21 (20.79%)

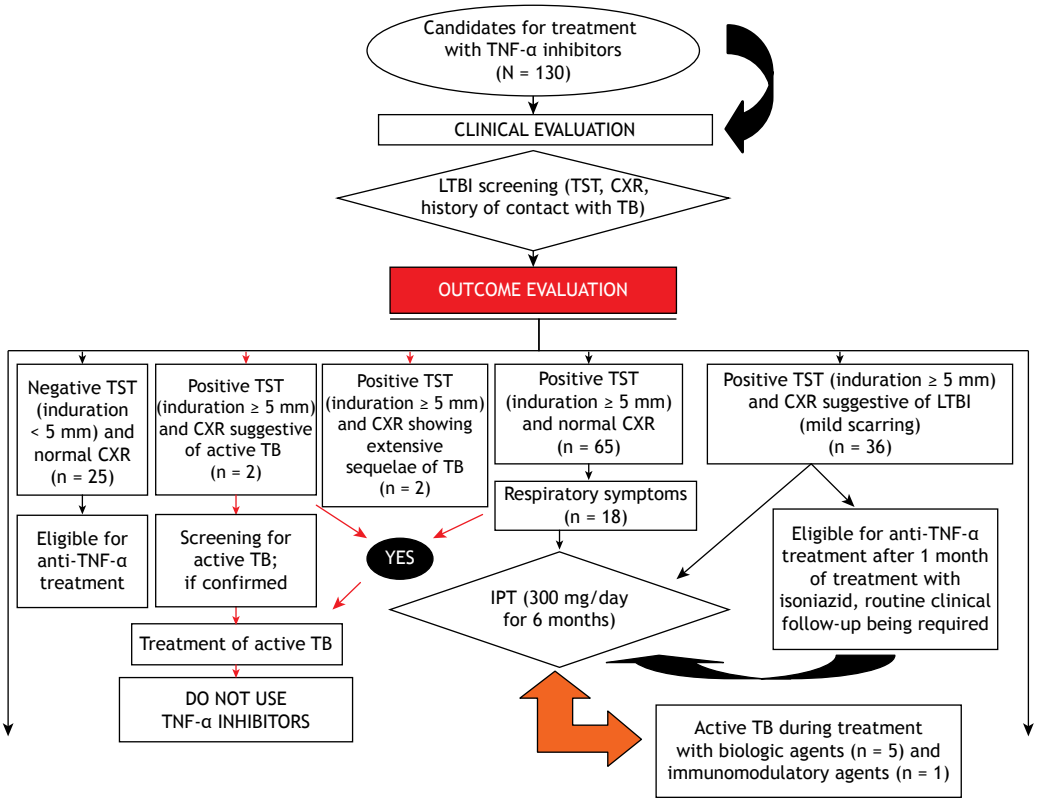

Figure 1. Flow chart of latent tuberculosis infection (LTBI) screening outcomes among candidates for treatment with TNF-α inhibitors. TST: tuberculin skin test; CXR: chest X-ray; TB: tuberculosis; and IPT: isoniazid preventive therapy.

were being treated with ≥ 15 mg of daily prednisone (mean daily dose, 12.540 ± 0.949 mg).

Most (n = 91; 90.09%) of the patients received IPT for 6 months. Of those 91 patients, 86 (94.50%) completed the treatment. Ten patients (9.90%) received IPT for 9 months. Therefore, 96 patients (95.05%) completed the prophylactic treatment. Of the remaining 5 patients, 4 (3.96%) discontinued IPT because of adverse reactions to isoniazid and 1 (0.99%) abandoned IPT (Table 2). Of the patients who received IPT, 84 (83.17%) had no adverse reactions to isoniazid. Of those, 83 (98.81%) completed the prophylactic treatment ($p = 0.002$). Only 1 patient (1.19%) abandoned IPT, at 2 months of treatment, because the decision to use biologic agents in that patient had to be reconsidered.

In 96 patients (95.05%), liver transaminase levels were found to be normal at 30 days of IPT. Of those 96 patients, 93 (96.88%) completed the treatment. Transient elevation of liver transaminases was observed in 5 patients (4.95%). Hepatotoxicity was observed in only 3 patients (2.97%). Of those, only 2 did not complete the treatment ($p = 0.001$; Table 2). Table 3 shows the results of our multivariate analysis of factors associated with completion of IPT.

Infliximab was the most widely used biologic agent, in 46 patients (58.23%), followed by etanercept, in 15 (18.99%), adalimumab, in 12 (15.19%), golimumab, in 1 (1.27%), and bevacizumab, in 1 (1.27%). Four patients (5.05%) used biologic agents having different immune targets, including rituximab, tocilizumab, abatacept, and ustekinumab. The mean follow-up period was 3.08 ± 0.13 years (range, 6 months to 4 years). At the end of the study period, 68 patients (86.07%) had been receiving treatment with biologic agents for more than 1 year, and 46 (58.23%) received treatment for 4 years.

By the end of the study, active tuberculosis had been diagnosed in 5 patients receiving treatment with biologic agents and in 1 patient receiving treatment with immunomodulatory or immunosuppressant agents. Of those 6 patients, 5 were diagnosed with pulmonary tuberculosis and 1 was diagnosed with extrapulmonary tuberculosis. All 6 were cured. The mean duration of treatment with anti-TNF biologic agents before the onset of symptoms of active tuberculosis was 24.0 ± 8.09 months (range, 3-16 weeks). Of the 5 patients receiving treatment with biologic agents, 4 had rheumatic disease, 4 were using infliximab, 1 was using etanercept, and all tested positive for LTBI (Figure 2).

The relative risk of developing active tuberculosis was 1.39 times higher (95% CI: 0.17-11.3) in patients treated with biologic agents (78.22%) than in those not treated with biologic agents (21.78%). In addition, it was 3.15 times higher (95% CI: 0.38-25.9) in patients using prednisone (61.38%) than in those not using

Table 1. Demographic, epidemiological, and clinical characteristics of the study patients.[a]

Variable	Total (N = 101)	Biologic agents (n = 79)	Immunosuppressants (n = 22)	p*
Sex				
Male	46 (45.54)	40 (86.96)	6 (13.04)	0.051
Female	55 (54.46)	39 (70.91)	16 (29.09)	
Age, years				
Male	45.40 ± 2.13			0.002
Female	53.16 ± 1.76			
Age group, years				
< 40	25 (24.75)	21 (84.00)	4 (16.00)	
40-59	52 (51.49)	40 (76.92)	12 (23.08)	
≥ 60	24 (23.76)	18 (75.00)	6 (25.00)	
BCG vaccination				
Yes	83 (82.18)	64 (81.01)	19 (86.36)	0.075
No	18 (17.82)	15 (18.99)	3 (13.64)	
History of contact with a tuberculosis case				
Yes	39 (38.61)	30 (76.92)	9 (23.08)	0.803
No	62 (61.39)	49 (79.03)	13 (20.97)	
History of tuberculosis treatment				
Yes	10 (9.90)	9 (90.00)	1 (10.00)	0.068
No	91 (90.10)	70 (76.92)	21 (23.08)	
Respiratory symptoms				
Yes	18 (17.82)	15 (83.33)	3 (16.67)	0.075
No	83 (82.18)	64 (77.11)	19 (22.89)	
Chest X-ray				
Abnormal	36 (35. 64)	27 (75.0)	9 (25.0)	0.560
Normal	65 (64.36)	52 (80.0)	13 (20.0)	
Tuberculin skin test induration, mm				
5-10	48 (47.52)	38 (48.10)	10 (45.45)	
>10	53 (52.48)	41 (51.90)	12 (54.55)	
Tuberculin skin test induration, mm				
5-10	7.31 ± 0.28			0.0001
> 10	16.36 ± 0.70			
Clinical diagnosis				
Rheumatic disease	84 (83.17)	64 (76.19)	20 (23.81)	
Skin disease	9 (7.92)	9 (100.0)	0 (0.00)	
Gastrointestinal disease	8 (8.91)	6 (75.00)	2 (25.0)	

[a]Values expressed as n (%) or mean ± SD. *Two-tailed Pearson's chi-square test with Yates' correction. The two-tailed Fisher's exact test was used for contingency tables with fewer than five cells. The Student's t-test was used for means and SDs.

prednisone (38.61%). Furthermore, it was 7.95 times higher (95% CI: 0.96-65.50) in patients with a history of contact with a tuberculosis case (38.61%) than in those without such a history (61.39%; Table 4).

DISCUSSION

Treatment with TNF inhibitors has been reported to increase the risk of active tuberculosis by 1.6- to 25.1-fold.[8] In our study, the risk of developing active tuberculosis was 1.39 times higher in patients who received treatment with biologic agents than in those who did not. Because of this risk, special emphasis has been given to the importance of LTBI treatment in endemic countries, such as Brazil. However, there is insufficient evidence for the efficacy of different prophylactic treatment regimens for LTBI. Most developing countries recommend 9 months of IPT (the 9H regimen). However, alternative regimens such as 3 months of treatment with rifampin and isoniazid (the 3RH regimen) and 4 months of treatment with rifampin result in less hepatotoxicity and better adherence to treatment than does the 9H regimen. Nevertheless, there is little evidence supporting their clinical efficacy. The 3RH regimen has been shown to be equivalent to 6 months of isoniazid treatment (the 6H regimen) and the 9H regimen in terms of efficacy and safety, its use being recommended by the World Health Organization.[9]

Lee et al.[8] reported that, despite prophylactic treatment, 5 patients developed active tuberculosis

Table 2. Variables associated with isoniazid preventive therapy (N = 101).[a]

Variable	Total	Completed the treatment	Did not complete the treatment	p
Duration of IPT				
6 months	91 (90.09%)	86 (94.50)	5 (5.49)	
9 months	10 (9.90 %)	10 (100.0)	0 (0.00)	
≥ 1 month of IPT before treatment with				
Biologic agents	79 (78.21)	78 (98.73)	1 (2.27)	0.001
Other immunosuppressants	22 (21.78)	18 (81.82)	4 (18.28)	
Adverse reactions to isoniazid				
Yes	17 (16.83)	13 (76.47)	4 (23.53)	0.002
No	84 (83.17)	83 (98.81)	1 (1.19)	
ALT levels at 30 days of IPT				
Normal	96 (95.05)	93 (96.88)	3 (3.12)	0.001
Abnormal	5 (4.95)	3 (60.0)	2 (40.0)	
AST levels at 30 days of IPT				
Normal	96 (95.05)	93 (96.88)	3 (3.12)	0.001
Abnormal	5 (4.95)	3 (60.0)	2 (40.0)	

IPT: isoniazid preventive therapy; ALT: alanine aminotransferase; and AST: aspartate aminotransferase. [a]Values expressed as n (%). *Fisher's exact test.

Table 3. Multivariate analysis of factors associated with completion of isoniazid preventive therapy.

Variable	OR (95% CI)	p
Drug treatment		
Biologic agents	17.3 (1.82-164.5)	0.0130
Other immunosuppressants (prednisone)		
Treatment with methotrexate		
Yes	1.63 (0.26-10.1)	0.6013
No		
Adverse reactions		
Yes	25.53 (2.64-246.7)	0.0051
No		
ALT levels		
Normal	20.60 (2.46-173.3)	0.0053
Abnormal		

ALT: alanine aminotransferase.

during follow-up; however, all 5 were treated with the 9H regimen, which was related to isoniazid resistance. In our study, 5 patients developed active tuberculosis despite IPT with the 6H regimen. Coskunol et al.[10] found that 5 patients receiving anti-TNF-α therapy developed active tuberculosis; of those, 3 had ulcerative colitis and 2 had ankylosing spondylitis. All 5 were using infliximab. Of the 5 patients, 4 were diagnosed with pulmonary tuberculosis and 1 was diagnosed with extrapulmonary tuberculosis. The time from initiation of anti-TNF-α therapy to tuberculosis infection was 6 months, in 3 patients; 15 months, in 1; and 24 months, in 1. In our study, the time from initiation of anti-TNF-α therapy to tuberculosis infection ranged from 10 months to 48 months. These results show that tuberculosis cannot be completely prevented during treatment with TNF inhibitors, even in patients receiving preventive treatment for LTBI. Therefore, the possibility of tuberculosis should always be considered.[4]

In a classic study published in 2001, Keane et al.[11] examined the role of treatment with biologic agents in the occurrence of opportunistic infections by analyzing cases of tuberculosis after treatment with infliximab. During the study period, there were 70 reported cases of tuberculosis after treatment with infliximab, for a median of 12 weeks. In a study of data from a Brazilian national registry of biologic agent use in patients with rheumatoid arthritis, 750 patients treated with biologic agents were compared with 287 controls receiving treatment with immunosuppressive agents.[12] There were 3 confirmed cases of tuberculosis in the group of patients treated with biologic agents, a finding that underscores the importance of continuously monitoring biologic agent use. Infliximab was the most commonly used TNF inhibitor,[12] a finding that is consistent with ours.

According to Lee et al.,[13] prophylactic treatment significantly reduces the risk of tuberculosis, with

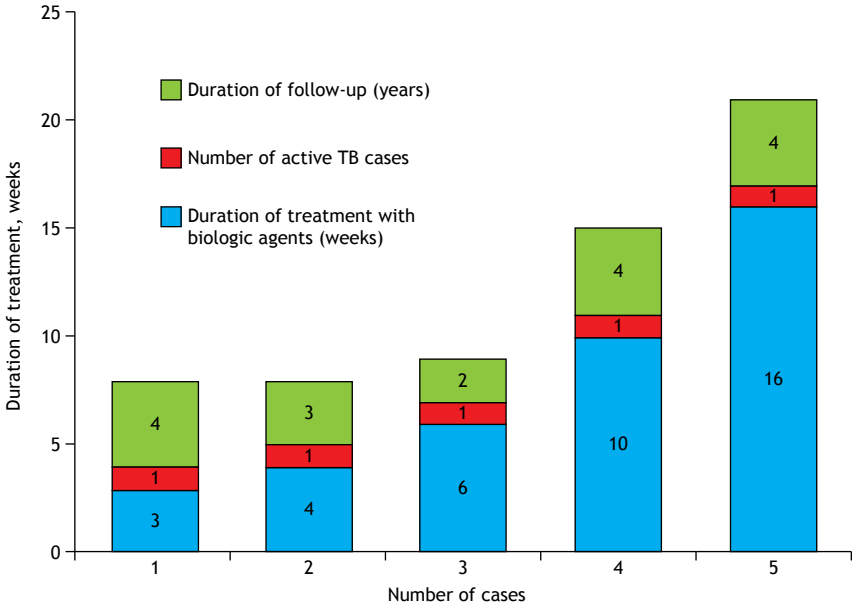

Figure 2. Cases of active tuberculosis (TB) during treatment with biologic agents.

Table 4. Relative risk of developing tuberculosis.

Variable	n (%)	Cases of active tuberculosis, n	RR	95% CI	p
Biologic agent use	79 (78.22)	5	1.39	0.17-11.3	0.7567
Immunosuppressant use	22 (21.78)	1			
Methotrexate use	52 (51.48)	2	0.47	0.09-2.46	0.3719
No methotrexate use	49 (48.51)	4			
Prednisone use	62 (61.38)	5	3.15	0.38-25.9	0.2870
No prednisone use	39 (38.61)	1			
History of contact with tuberculosis	39 (38.61)	5	7.95	0.96- 65.5	0.0541
No history of contact with tuberculosis	62 (61.39)	1			
Abnormal chest X-ray	36 (35.64)	2	0.90	0.17-4.69	0.9032
Normal chest X-ray	65 (64.36)	4			
TST induration = 5-10 mm	48 (47.52)	2	0.55	0.11-2.88	0.4809
TST induration ≥ 10 mm	53 (52.48)	4			

RR: relative risk; and TST: tuberculin skin test.

an incidence rate of 0.33. Therefore, LTBI treatment significantly reduces the risk of developing active tuberculosis and tuberculosis transmission in the community. This means that LTBI diagnosis and treatment constitute a strategy to eliminate active tuberculosis, preventing new cases. Long-term studies have shown that IPT for 3, 6, and 12 months reduces the risk of developing active tuberculosis by 21%, 65%, and 75%, respectively.[14] Treatment adherence has been recognized as a critical parameter, treatment efficacy being highest when at least 80% of doses are administered.[14]

According to Tost et al.,[15] a tuberculosis treatment regimen is useful when more than 95% of patients are cured and less than 5% develop severe intolerance. In our study, patients received IPT for 6 months, with a high treatment completion rate (> 90.0%) and a low treatment abandonment rate (0.99%). With regard to the safety of isoniazid, adverse effects were uncommon; transient adverse effects were reported in only 16.83% of the sample, a finding that is consistent with those of another study,[16] and hepatotoxicity was observed in only 2.97%. These data are promising because the study patients had immune-mediated chronic inflammatory diseases and were receiving treatment with immunosuppressive or immunomodulatory agents, as well as having associated comorbidities.

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SPECIAL ARTICLE

Exploratory analysis of requests for authorization to dispense high-cost medication to COPD patients: the São Paulo "protocol"

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ABSTRACT

Objective: A resolution passed by the government of the Brazilian state of São Paulo established a protocol for requesting free COPD medications, including tiotropium bromide, creating regional authorization centers to evaluate and approve such requests, given the high cost of those medications. Our objective was to analyze the requests received by an authorization center that serves cities in the greater metropolitan area of (the city of) São Paulo between 2011 and 2016. **Methods:** Data regarding the authorization, return, or rejection of the requests were compiled and analyzed in order to explain those outcomes. Subsequently, the clinical and functional data related to the patients were evaluated. **Results:** A total of 7,762 requests for dispensing COPD medication were analyzed. Requests related to male patients predominated. Among the corresponding patients, the mean age was 66 years, 12% were smokers, 88% had frequent exacerbations, and 84% had severe/very severe dyspnea. The mean FEV_1 was 37.2% of the predicted value. The total number of requests decreased by 24.5% from 2012 to 2013 and was lowest in 2015. Most (65%) of the requests were accepted. The main reasons for the rejection/return of a request were a post-bronchodilator FEV_1/FVC ratio > 0.7, a post-bronchodilator FEV_1 > 50% of the predicted value, and failure to provide information regarding previous use of a long-acting β_2 agonist. During the study period, the total number of requests returned/rejected decreased slightly, and there was improvement in the quality of the data included on the forms. **Conclusions:** Here, we have identified the characteristics of the requests for COPD medications and of the corresponding patients per region served by the authorization center analyzed, thus contributing to the improvement of local public health care measures.

Keywords: Pulmonary disease, chronic obstructive; Clinical protocols; Drug costs; Tiotropium bromide.

INTRODUCTION

Worldwide, COPD is responsible for the high use of health care resources due to the high rates of morbidity and mortality of the disease.[1] It is the fourth leading cause of death in the world,[2] and it is estimated that there are 7 million individuals with COPD in Brazil.[1,3] According to data from the *Departamento de Informática do Sistema Único de Saúde* (SUS, Unified Health System), annual expenditures related to hospitalizations due to COPD in Brazil have remained above R$ 100 million every year since 2011. In 2017, there were 119,000 COPD-related hospitalizations, with a total expenditure of R$ 108 million.[4]

Given COPD evolution and prognosis, the focus of its treatment is to reduce symptoms and slow down the progression of the disease, improving dyspnea, exercise tolerance, and quality of life. In addition, exacerbations should be prevented and treated, reducing the number of hospitalizations.[2,5,6]

Non-pharmacological and pharmacological treatment is established in accordance with national and international guidelines,[2,7] the pillars of treatment being the use of long-acting bronchodilators. The evolution in the knowledge of the disease and in clinical research resulted in the introduction of new drugs for the treatment of COPD. However, the unrestricted incorporation of new treatments represents a high cost to SUS, especially regarding high-prevalence diseases.

The São Paulo State Department of Health, by means of Resolution no. 278 of July 26, 2007,[8] introduced a protocol for the free treatment of patients with COPD for the first time in Brazil. The protocol innovatively established free hierarchical treatment for all severity levels of the disease, including the rational use of long-acting β_2

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agonists (LABA) and long-acting muscarinic antagonists (LAMA), allowing access to treatment of a greater number of patients by SUS. In addition, São Paulo pioneered the introduction of tiotropium bromide into the therapeutic arsenal for the treatment of COPD in Brazil. Resolution no. 278[8] also included a set of criteria and documents necessary for the request of COPD medications, creating 13 authorization centers (universities or hospitals of the state network), indicated by the *Sociedade Paulista de Pneumologia e Tisiologia* (São Paulo Thoracic Association), which cover practically all the regional health care divisions in the state. The processes/completion of request forms initiate in the *Farmácias de Medicamentos Especializados* (Specialized Drug Pharmacies) in the referral areas and are sent to the authorization centers. One of those centers is located in the *Instituto do Coração* of the *Hospital das Clínicas*, *Faculdade de Medicina da Universidade de São Paulo* (InCor-HC-FMUSP), located in the city of São Paulo, which serves 38 municipalities grouped into five regions (Chart 1), with a resident population of more than 8 million people. To our knowledge, this center serves the greatest number of patients.

According to one study,[1] the mean prevalence of COPD is 16% in the population over 45 years of age, and 70% of that population have yet to be diagnosed with the disease and, therefore, have received no treatment. Thus, we can infer that the set of those 38 municipalities had an approximate population of over half a million untreated adults in 2015. According to data from the *Departamento de Informática do* SUS,[4] in that set of municipalities, the mortality rate due to COPD per 100,000 population showed a trend toward an increase between 2011 and 2015.

As of 2015, with the publication of the technical note of the *Grupo de Assistência Farmacêutica da Coordenadoria de Ciência, Tecnologia e Insumos Estratégicos de Saúde* (GAF/CCTIES, Pharmaceutical Assistance Group of the Coordination of Science, Technology, and Strategic Health Supplies) no. 02 of January 15, 2015,[9] the flow for COPD drug dispensing was standardized, including a medical report called "Annex B: Tiotropium Request Medical Report" that included clinical and functional data of the patients. This guideline is used throughout the state of São Paulo and involves the 13 authorization centers.

The objective of the present study was to analyze the characteristics of tiotropium bromide requests for the treatment of COPD received between 2011 and 2016, based on data from the decisions of expert physicians of the InCor-HC-FMUSP authorization center. Reasons for the return or refusal of medication requests were assessed in an attempt to identify the major difficulties in complying with the protocol. The secondary objective was to determine the clinical and functional profile of the COPD patients by means of the data available on specific tiotropium bromide requests and medical reports received between 2015 and 2016.

METHODS

As of 2011, the InCor-HC-FMUSP authorization center systematized the collection of data regarding the evaluation reports on the medication requests, compiling the reasons for the decision making (approval, return, or rejection) in a spreadsheet. After the publication of the technical note GAF/CCTIES no. 02[9] and the adoption of Annex B, which contains clinical and functional data of the patients, those data were also compiled in the database.

The following variables were collected: evaluation report results; reasons for returns or rejections (insufficient or erroneous data); age; International Classification of Diseases (10th edition) code[10]; disease duration; smoking history; influenza and/or pneumococcal vaccination; previous pharmacological treatment; clinical assessment of dyspnea (modified Medical Research Council scale); exacerbations; and lung function data.

A descriptive analysis of the collected data was carried out, evaluating the number of requests per region over time. The reasons for approval and the temporal evolution of this decision were evaluated. As of 2015, the clinical and functional profile of those patients was determined, based on the reports (Annex B). The descriptive statistical analysis was performed using Excel 2013, Sigma Stat, version 3 (Systat Software,

Chart 1. *Farmácias de Medicamentos Especializados* (Specialized Drug Pharmacies) by region and coverage of municipalities served by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*.

Region	Municipalities	Total population/ region, 2016
FRANCO DA ROCHA	Caieiras, Cajamar, Francisco Morato, Franco da Rocha, Mairiporã	581,464
MOGI DAS CRUZES	Arujá, Biritiba-Mirim, Ferraz de Vasconcelos, Guararema, Itaquaquecetuba, Mogi das Cruzes, Poá, Salesópolis, Santa Isabel, Suzano	1,593,224
GUARULHOS	Guarulhos	1,337,087
SANTO ANDRÉ (ABC-Hospital Estadual Mário Covas)	Diadema, Mauá, Ribeirão Pires, Rio Grande da Serra, Santo André, São Bernardo do Campo, São Caetano do Sul	2,736,683
OSASCO	Barueri, Carapicuíba, Cotia, Embu, Embu-Guaçu, Itapecerica da Serra, Itapevi, Jandira, Juquitiba, Osasco, Pirapora do Bom Jesus, Santana do Parnaíba, São Lourenço da Serra, Taboão da Serra	2,906,759

Inc., San José, CA, USA), and DMSS, version 18 (DMSS Software, São Paulo, Brazil). The project was approved by the research ethics committee of the institution (CAAE no. 67319817.5.0000.006).

RESULTS

Between 2011 and 2016, 7,762 request forms were analyzed—an annual average of 1,293 requests. The total number of requests per year/region is described in Figure 1. Most requests were issued in the ABC and Osasco regions—3,085 and 2,429 requests, respectively—being responsible for 71% of the requests. Taking into account all municipalities, the total number of requests decreased by 24.5% from 2012 to 2013 and was lowest in 2015. The mean number of requests per 100,000 population/year per region can be seen in Figure 2.

Although most of the requests were authorized between 2011 and 2016, 35% were initially returned or rejected because of the reasons described in Chart 2. The total number of returned or rejected requests showed a slight reduction during the study period (from 38% in 2011 to 35% in 2016). Rejection or return of the requests was often due to more than one reason. However, the most common reasons were as follows: a post-bronchodilator FEV_1/FVC ratio > 0.7; a post-bronchodilator FEV_1 > 50% of the predicted value; and failure to provide information regarding previous treatment with a LABA, as defined in the Resolution.

Over time, there was an improvement in the completion of the forms, mainly represented by a decrease in the requests with no spirometry results, lack of prescription, inadequate dosing schedule, or failure to provide information regarding the previous treatment with a LABA. The latter reason was responsible for 135 and 56 returned requests in 2011 and 2016, respectively. The year 2015 was critical in relation to the absence or incompleteness of a specific medical

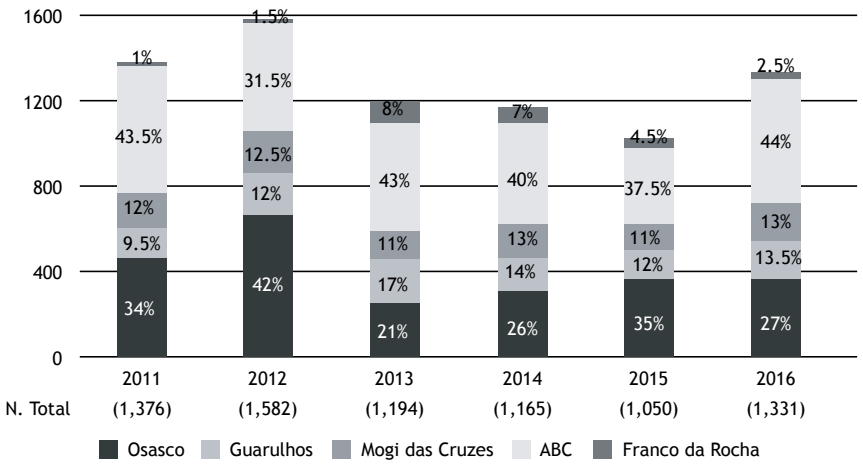

Figure 1. Total annual requests received by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* by region, 2011-2016 (N = 7,762).

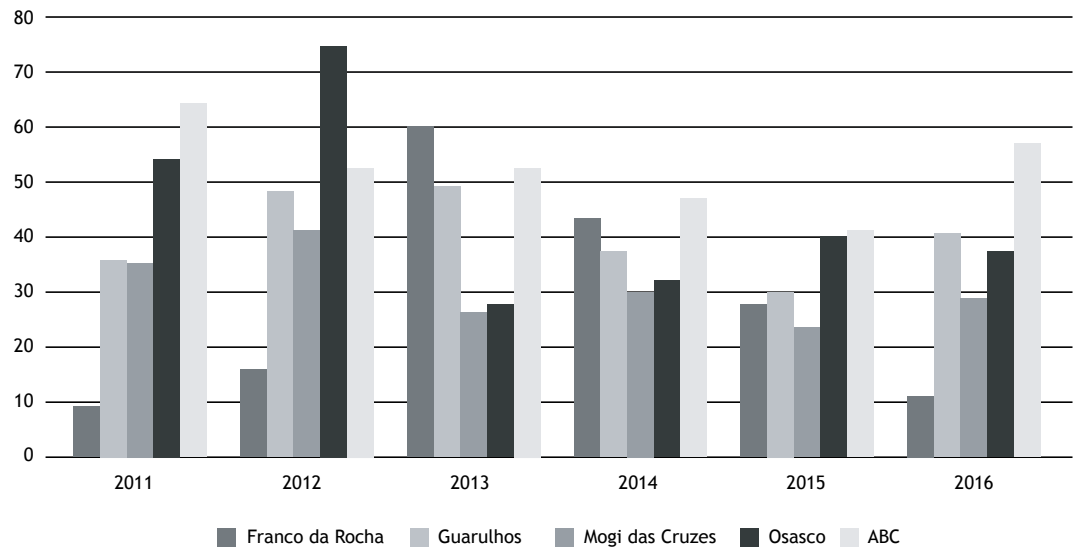

Figure 2. Annual rate of requests received by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* by region per 100,000 population, 2011-2016 (N = 7,762).

report enclosed in the tiotropium bromide request. It should be noted that the proportion of returns/rejections due to an FEV_1/FVC ratio > 0.7 remained similar during the study period. The proportion of reasons for returns/rejections per year between 2011 and 2016 can be seen in Figure 3.

The profile of patients whose requests were authorized (n = 2,317) between 2015 and 2016 is shown in Table 1. Requests related to male patients predominated. Among the corresponding patients, the mean age was 66 years. The most common code of the International Classification of Diseases (10th version) was J44 (96% of all requests). The data showed that 12% of the patients were smokers at the time of the request. According to the medical reports, only 15% received drug therapy for smoking cessation, and the mean time since smoking cessation was 10.0 ± 9.4 years. In addition, the reports revealed a high prevalence of patients that had exacerbations, 88% being diagnosed with frequent exacerbations (two or more exacerbations in the last year). The analysis of dyspnea severity showed very symptomatic patients—modified Medical Research Council scores ≥ 3 in 84% of the patients. The mean FEV_1 was 37.2% of the predicted value, demonstrating severe functional limitation in the patients whose requests were accepted (Table 1).

Chart 2. Reasons for returning/rejecting tiotropium bromide requests by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*, 2011-2016.

Reason
1. Lack of spirometry results
2. Post-bronchodilator FEV_1 > 50% of the predicted value
3. Post-bronchodilator VEF_1/CVF > 0.7
4. Lack of or incomplete medical report
5. No information on previous use of a long-acting β_2 agonist
6. Lack of or inadequate dosage prescription

DISCUSSION

The present study shows the analysis of data available in the medication requests for COPD treatment in the public health care system of the state of São Paulo received by the InCor-HC-FMUSP authorization center between 2011 and 2016. It was possible to analyze the reasons for returns or rejections of the requests, the most common ones being failure to provide information regarding spirometry or post-bronchodilator FEV_1 > 50% of the predicted value.

Resolution no. 278,[8] modified over time, was based on a protocol comprising inclusion criteria and a flow chart indicating the prescription of each group of medications that had been previously selected in a SUS referral center for the treatment of COPD patients.[11] The protocol used the recommendations of the best evidence available at the time, indicating the need to introduce new medications, such as tiotropium bromide, in order to preserve treatment efficacy according to the severity of COPD. In 2007, the state of São Paulo was a pioneer in the implementation of that protocol, which already recommended the use of a long-acting bronchodilator plus a short-acting bronchodilator in patients with COPD who remained symptomatic and emphasized that the treatment should be adapted to local conditions, considering the resources available and the clinical characteristics of the patients.

The importance of tiotropium bromide in the treatment of COPD has also been demonstrated in various randomized trials and in a real-life study.[6] The combination of tiotropium bromide, which is a bronchodilator classified as a LAMA, is beneficial in patients with severe and very severe COPD. The use of

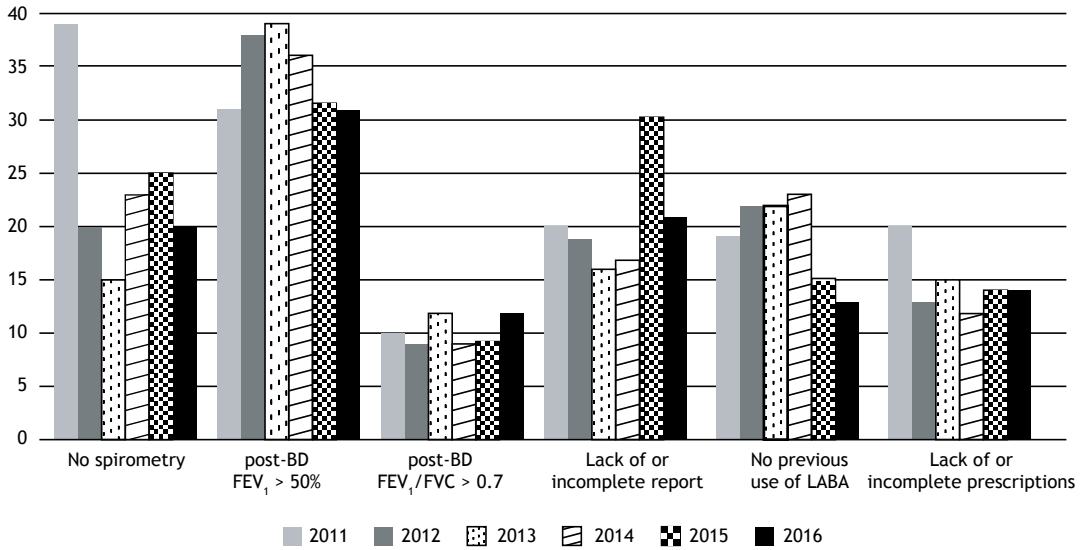

Figure 3. Annual proportion of returns/rejections of requests received by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* according to the main outcomes, 2011-2016 (N = 2,718). post-BD: after the use of bronchodilator; and LABA: long-acting β_2 agonists.

Table 1. Characteristics of the patients whose requests for the dispensing of tiotropium bromide were accepted by the authorization center in the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*. 2011-2016.[a]

Characteristic	Result
Male gender, %	52
Age, years	66.0 ± 10.6
Disease duration	9.5 ± 7.4
Smoker	171 (12)
Former smoker	1,259 (87)
Smoking history, pack-years	42 ± 12
Influenza vaccination, %	84
Pneumococcal vaccination, %	16
Exacerbation in the last year, %	94
≥ 2 exacerbations in the last year, %	88
mMRC scale score, %	
1	3
2	13
3	52
4	32
FEV_1, L	1.0 ± 0.9
FEV_1, % predicted	37.2 ± 2.0

mMRC*: modified Medical Research Council*.
[a]Values expressed as n (%) or as mean ± SD, except where otherwise indicated.

a LAMA alone as an initial treatment or its association with a LABA is indicated in patients with COPD and moderate obstructive lung disease.[7]

After the state of São Paulo, Espírito Santo (2009),[12] Minas Gerais (2010),[13] Ceará (2010),[14] the Federal District (2012),[15] and Pernambuco (2013)[16] also implemented the dispensing of tiotropium bromide, using specific protocols. The protocol of the state of São Paulo was used as a reference, incorporating the specificities of each region.

In 2013, a study in Canada analyzed the impact of implementing public drug dispensing policies for COPD patients in British Columbia between 2007 and 2009.[17] Initially, there was an increase in total costs; however, there was a reduction in the costs paid by the patient himself/herself and his/her private insurance companies: a 19% drop ($ 2.97 million Canadian dollars) in total spending on medications.[17]

In the elaboration of the São Paulo protocol that gave rise to Resolution no. 278,[8] an additional cost of R$ 400 million/year was estimated due to the dispensing of tiotropium bromide. The costs were estimated based on the prevalence of severe patients,[1] resulting in discussions regarding the financial impact of the free dispensing of that medication and strengthening the debate for the inclusion of technical analyses of the requests, which made the implementation of the protocol viable. The use of rational dispensing based on well-defined criteria and authorization centers has reduced the costs to approximately one quarter of the predicted value. Considering the characteristics of the population and the access to medications, it is relevant that the protocol and the resolution of the state of São Paulo guaranteed access of the population with severe/very severe COPD to the medication.

The variations in the rates of requests per 100,000 population in the different regions can be due to various factors. However, we have no information on the regional characteristics regarding health care services and access to the exams in those regions, although the mapping of future public health care actions is of great value, even to analyze the impact of such factors on treatment protocols.

The implementation of protocols with well-established criteria for dispensing medications can significantly contribute with data to public health care managers and rationalize access to treatment. Here, the administrative flow of requests, authorization center evaluations, and outcomes (approval, return, or rejection) refers only to the dispensing of tiotropium bromide. The other medications provided for in the protocol are authorized locally, with no need for the systematic control of their use.

In 2015, the technical note GAF/CCTIES no. 2[9] addressed the need for document standardization for dispensing medications, including the standardized medical report for tiotropium bromide requests. That model has met the needs for verification, in a structured way, regarding the criteria[9] defined in the protocol. The elaboration of a database containing such information allowed the characterization of the population involved in that protocol. It is important to note that, although prior knowledge of medication dispensing rules might create a bias in completing the request form, 35% of those were initially returned or rejected due to noncompliance with protocol criteria, signaling the need for a specific audit.

Our data revealed that the mean age of the patients was 66 years, and most were males, ex-smokers, and very symptomatic. In addition, there was a high prevalence of influenza vaccination, exacerbations, and severe functional impairment.

The data in the medical reports indicated that more than 80% of the patients received influenza vaccine; however, only 16% received pneumococcal vaccine. This information was collected from data filled out by physicians retrospectively and, probably, based on patient self-report. The use of influenza and pneumococcal vaccination in the elderly with chronic lung disease showed significant reductions in the risk of hospitalization due to pneumonia and of death, respectively (from 52% to 72% and from 70% to 82%).[18] This shows the need to disclose the benefits of pneumococcal vaccination to COPD patients and to the health professionals who serve them.

Patients with COPD usually have one or two exacerbations per year, especially during winter.[18] In the present study, 88% of the patients had two or more exacerbations/year. Although this information was probably collected from patient self-reports, it might indicate that this group of patients require frequent

medical care. We highlight that a Brazilian study published in 2017[19] pointed to important indicators in COPD patients with exacerbations: in-hospital mortality during exacerbation, 3.6%-11.0%; risk of hospitalization in the year following hospitalization, 23-43%; and calculated fatality (excess mortality compared with stable COPD), 15.6%. This highlights the importance of measures to prevent and treat COPD exacerbations.

Due to the high cost of tiotropium bromide compared with that of LABA or LABA + inhaled corticosteroid, the protocol stipulated that tiotropium should be used as a second-line medication. Thus, in the present study, all of the requests accepted indicated the prior use of LABA, a criterion to be met for tiotropium bromide dispensing. The failure to inform that as an initial reason for rejection was 19% and 13% in 2011 and 2016, respectively, which may signal an increasing learning curve of the physicians in relation to the protocol criteria.

Spirometry is an essential test for the definitive diagnosis of COPD,[2] and FEV_1 is one of the criteria for the approval of tiotropium bromide requests. In the present study, the lack of spirometry results in the requests as a reason for their return/rejection fell from 39% in 2011 to 19% in 2016. This fact might indicate a better knowledge of the protocol criteria during time, or eventually, that there was greater access to spirometry. This is relevant since the underuse of spirometry has been reported to be a determining factor in the underdiagnosis of COPD.[5] Underuse of spirometry was also identified in a Latin-American study,[1] in which only 20% of the patients with COPD had performed previous spirometry. This is probably due to the lack of resources for equipment availability, lack of patient access to the test, or even lack of knowledge on the part of health professionals. It is also worth mentioning that approximately 10% of the requests were returned/rejected each year due to spirometry results that showed no obstructive disorder. At the moment, we have no access to information in order to verify unbiasedly whether the origin of those requests came from professionals specializing in pulmonology or not.

It is impossible to know the subsequent follow-up of the patients who received the medications by the analysis of the request forms. Renewals are dispensed directly by the requesting site; therefore, the authorization center has no information regarding the universe of patients who benefited from the treatment and those whose response was inadequate; for the latter, we should consider the possibility of discontinuation of the medication and search for therapeutic alternatives.

To our knowledge, this is the first study that presents data regarding medication requests related to Resolution no. 278,[8] and some limiting factors must be taken into account. The analysis is based on retrospectively completed data included on the tiotropium bromide requests. The authorization center has no control over how this information is collected, and prior knowledge of the medication dispensing criteria could eventually create a bias in the completion of the reports. We also have no information related to factors such as availability of professionals for patient health care, physician knowledge about the protocol, access to spirometry, among others.

Implementing and meeting protocol criteria for dispensing medications is an important guide in the clinical practice. The essential action for the promotion of health, as recommended by the World Health Organization,[20] indicate that the rational use of medications is one of the most important components of the policies promoted by the Organization.

In summary, the analysis of the data allowed us to identify the characteristics of the requests for tiotropium bromide and of the corresponding patients per region served by InCor-HC-FMUSP authorization center (38 municipalities) between 2011 and 2016, which can contribute to the optimization of specific and local public health care measures. Data from authorization centers are living records of COPD morbidity in the country, and the publication of those data might prompt reflection to authorization centers in the state of São Paulo and in other states and stimulate the publication of data collected in those centers.

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Intensity of physical exercise and its effect on functional capacity in COPD: systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the effects of high-intensity interval training (HIIT), in comparison with those of continuous exercise, on functional capacity and cardiovascular variables in patients with COPD, through a systematic review and meta-analysis of randomized controlled trials. **Methods:** We searched PubMed, the Physiotherapy Evidence Database, the Cochrane Central Register of Controlled Trials, and EMBASE, as well as performing hand searches, for articles published up through January of 2017. We included studies comparing exercise regimens of different intensities, in terms of their effects on functional capacity and cardiovascular variables in patients with COPD. **Results:** Of the 78 articles identified, 6 were included in the systematic review and meta-analysis. Maximal oxygen consumption (VO_{2max}) did not differ significantly between HIIT and control interventions. That was true for relative VO_{2max} (0.03 mL/kg/min; 95% CI: −3.05 to 3.10) and absolute VO_{2max} (0.03 L/min, 95% CI: −0.02 to 0.08). **Conclusions:** The effects of HIIT appear to be comparable to those of continuous exercise in relation to functional and cardiovascular responses. However, our findings should be interpreted with caution because the studies evaluated present a high risk of bias, which could have a direct influence on the results.

Keywords: Pulmonary disease, chronic obstructive; Exercise; Oxygen consumption.

INTRODUCTION

Because COPD has systemic involvement and is an important risk factor for other comorbidities, it has a growing impact worldwide,[1] and chronic airflow limitation due to abnormality in the alveolar airways is its most striking characteristic, the major symptom of which is dyspnea,[2] resulting from genetic deficiency (alpha-1 antitrypsin deficiency), outdoor or indoor air pollution (related to firewood burning), significant exposure to noxious particles or gases (such as cigarette smoke), etc. However, COPD can no longer be considered a disease presenting with pulmonary involvement alone.[3]

Exercise intolerance is a consequence of COPD, leading the patient to a sedentary lifestyle to avoid exercise-induced dyspnea. The association of physical inactivity with the metabolic disorders and structural changes caused by the disease, as well as the fact that smoking is also a primary cause, results in there being multiple risk factors for cardiovascular disease in this population.[4] In addition, COPD is a powerful independent risk factor for cardiovascular morbidity and mortality,[5] since the major risk factors for cardiovascular disease are also present in these patients.[6]

Physical exercise is an integral part of pulmonary rehabilitation programs. The principles of training are exercise duration, frequency, progression, modality, individualization, and, especially, intensity, which is recognized as the key determinant of the physiological benefits gained from rehabilitation.[7] According to the American College of Sports Medicine,[8] moderate-intensity continuous aerobic exercise for 20 to 60 min per session brings physiological benefits, whether on a treadmill or a cycle ergometer, the latter resulting in lower exercise-induced oxygen desaturation in the training of patients with COPD. High-intensity interval training (HIIT) can be an alternative to continuous exercise training for individuals with COPD who have difficulty reaching the target duration because of dyspnea, fatigue, or any other symptom.[9]

To date, there have been few studies correlating COPD and the effects of HIIT in pulmonary rehabilitation in terms of cardiovascular variables and functional capacity. One study describing the effects of two training programs in patients with COPD indicated improvement in functional capacity after 12 weeks of high-intensity training.[10] One study evaluating improvement in systolic function in patients with COPD reported that the effects of HIIT and of moderate exercise result in positive changes in cardiovascular values.[11] A study analyzing heart rate variability after HIIT in patients with COPD reported improvement in autonomic cardiac function after three months of HIIT.[12] In addition, a systematic review of studies on changes in ventilatory parameters in patients with moderate to severe COPD, who participated in pulmonary rehabilitation programs, evaluated exercise mode, frequency, duration, and intensity. Patients were shown to be able to perform HIIT, which resulted in positive changes in ventilatory parameters and in reduced exercise-related dyspnea.[13]

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Therefore, the present study plays an important role in improving scientific knowledge on the contributions of different intensities of aerobic exercise to cardiovascular health in individuals with COPD, given that the most recent systematic review on the subject was published in 2014 and evaluated only ventilatory outcomes. The objective of the present study was to systematically review the effects of HIIT, in comparison with those of continuous aerobic exercise or any other control intervention, on functional capacity and cardiovascular variables in patients with COPD.

METHODS

The study was conducted in accordance with the PRISMA Statement[14] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Protocol no. 42017056753).

Eligibility criteria and search strategy

We included randomized controlled trials that addressed the use of HIIT in patients with COPD, in comparison with the use of moderate-intensity continuous aerobic exercise or any other control intervention, on functional capacity, as measured by maximal oxygen consumption (VO_{2max}), six-minute walk distance (6MWD), and Borg dyspnea and leg fatigue scores, as well as on cardiovascular variables, such as endothelial function, ankle-brachial index, systolic blood pressure, diastolic blood pressure, HR, RR, and SpO_2. We included studies that used different HIIT modalities, such as treadmill or cycle ergometer training. We excluded articles that evaluated patients with an exercise-limiting disease or medical condition.

We searched the following electronic databases (from inception through January of 2017): PubMed; Physiotherapy Evidence Database; Cochrane Central Register of Controlled Trials; and EMBASE. In addition, we hand searched the references in published studies on the subject. Our search was performed on January 27, 2017 and included the keywords "high intensity interval training" and "pulmonary disease, chronic obstructive", as well as the corresponding keywords in Portuguese "*treinamento intervalado de alta intensidade*" and "*doença pulmonar obstrutiva crônica*". The keywords were combined with a sensitive list of terms for searching for randomized controlled trials that was compiled by Robinson & Dickersin.[15] Our search had no language restriction and was performed after the study had been registered with PROSPERO. Full articles published in journals and accepted papers were taken into account. The full search strategy used in PubMed is shown in Chart S1.

STUDY SELECTION AND DATA EXTRACTION

The titles and abstracts of all articles identified by the search strategy were evaluated independently and in duplicate by two reviewers. All abstracts that did not provide sufficient information about the inclusion and exclusion criteria were selected for full-text evaluation. In this second phase, the same reviewers independently evaluated the full texts and made their selections based on the pre-specified eligibility criteria. Disagreements between reviewers were resolved by consensus.

Using standardized electronic forms, the same two reviewers independently extracted data on the methodological characteristics of the studies, interventions, and results. Differences were again resolved by consensus.

Initially, the studies were assessed for the following: authors; year of publication; sample (total number of subjects); methodology; HIIT intervention protocol; control group; comparator protocol (if any); evaluated outcomes; results; and conclusions. The primary outcome extracted was VO_{2max} (in mL/kg/min and L/min). The secondary outcomes evaluated in the present study were 6MWD and the aforementioned cardiovascular variables.

Chart S1. Search strategy.

#1	"Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Pulmonary Disease, Chronic Obstructive" OR "COPD, Severe Early-Onset" OR "COPD" OR "Chronic Obstructive Pulmonary Disease" OR "COAD" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "Chronic Airflow Obstructions" OR "Chronic Airflow Obstruction"
#2	"High-Intensity Interval training"[Mesh] OR "High-Intensity Interval Training" OR "High Intensity Interval Training" OR "High-Intensity Interval Trainings" OR "Interval Training, High-Intensity" OR "Interval Trainings, High-Intensity" OR "Training, High-Intensity Interval" OR "Trainings, High-Intensity Interval" OR "High-Intensity Intermittent Exercise" OR "Exercise, High-Intensity Intermittent" OR "Exercises, High-Intensity Intermittent" OR "High-Intensity Intermittent Exercises" OR "Sprint Interval Training" OR "Sprint Interval Trainings" OR "Interval Training" OR "Interval Exercise" OR "Intermittent Exercise" OR "High Intensity Interval Exercise" OR "High Intensity Exercise" OR "High Intensity Training" OR "High Intensity Intermittent Exercises" OR "High-Intensity Exercise"
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])
#4	#1 AND #2 AND #3

Evaluation of risk of bias and data analysis

The evaluation of study quality was performed descriptively and included the following characteristics: adequate generation of randomization sequences; concealment of allocation; blinding; blinding of outcome assessors; intention-to-treat analysis; and reporting of losses and exclusions. All characteristics that were not clearly reported were classified as "no data".

The use of intention-to-treat analysis in a study was considered as confirmation that the number of randomized participants was the same as the number of analyzed participants. Studies without this characteristic were considered not to meet this criterion. Study quality was evaluated independently by the same two reviewers.

Meta-analysis was performed using the random-effects model, and effect measures were calculated as the mean difference between baseline and follow-up values. An α value = 0.05 was considered statistically significant. Statistical heterogeneity of treatment effect across studies was assessed using the inconsistency I^2 test, in which values above 25% and 50% were considered to be indicative of moderate and high heterogeneity, respectively. All analyses were conducted with the software Review Manager, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK).

RESULTS

The initial search identified 78 articles, of which 49 were retrieved for detailed analysis. Of those, 17 were considered potentially relevant. However, 11 studies were excluded: those by Nasis et al.,[16] Hsieh et al.,[17] Pitta et al.,[18] Rodríguez et al.,[19] and Varga et al.,[20] because they were quasi-experimental studies; that by Camilo et al.,[10] because the outcomes of interest were not reported; those by Probst et al.,[11] Puhan et al.,[12] and Pomidori et al.,[21] because the training performed was not consistent with the definition of HIIT; that by Mador et al.,[22] because the training did not fit within the upper limits defining HIIT; and that by Coppoolse et al.,[23] because HIIT was combined with another intervention. Therefore, 6 studies investigating a total of 295 patients were included in the systematic review and meta-analysis. Figure 1 provides a study inclusion flow chart, and Table 1 summarizes the characteristics of the included studies.

According to the inclusion criteria in the studies, the selected COPD patients were staged based on the presence of a post-bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of predicted and an FEV_1/FVC ratio $< 70\%$, as per the Global Initiative for Chronic Obstructive Lung Disease,[1] as having grade II or III disease (moderate or severe disease, respectively).[24-29]

Four studies compared HIIT with a rehabilitation program that included psychological support, endurance training, breathing exercises, COPD education, and relaxation (total sample of 238 individuals, of whom 140 were in the HIIT group).[24-27] One study compared HIIT with low-intensity continuous exercise,[28] whereas another 1 compared HIIT with moderate-intensity continuous exercise.[29]

Of the studies included in this systematic review, 4 (67%) had adequate randomization or reported randomization, having a low risk of bias; only 1 reported allocation concealment, and 1 reported blinding of outcome assessors, but only for one variable, having a high risk of bias; 5 described losses to follow-up and exclusions, having a low risk of bias; and none performed or reported intention-to-treat analysis, having a high risk of bias (Table 2).

In relation to the effects of the interventions, 3 studies[24,25,29] determined relative VO_{2max} (n = 200) and 3 studies[26-28] determined absolute VO_{2max} (n = 95). In both analyses, there was no significant difference between the HIIT groups and the control groups (relative VO_{2max} = 0.03 mL/kg/min; 95% CI: −3.05 to 3.10; I^2: 92%; and absolute VO_{2max} = 0.03 L/min; 95% CI: −0.02 to 0.08; I^2: 34%; Figures 2A and 2B).

On the basis of relative VO_{2max}, it is possible to identify similarities across studies,[24,25,29] especially in relation to the duration of each session (40, 39, and 38 min, respectively). Intervention duration ranged from 22 to 28 sessions. The type of training in the intervention group was similar across studies: aerobic cycling exercise[25]; aerobic exercise on a treadmill[29]; and aerobic exercise on a cycle ergometer.[24] However, the control groups are noteworthy: 2 studies[25,29] used a similar moderate-intensity intervention in the control group and reported no differences between the intervention and control groups; and 1 study[24] used a mix of interventions in the control group—patient education, drug therapy, breathing exercises, physical therapy, and nutrition—showing that the HIIT group was superior to the control group.

The studies[26-28] that determined absolute VO_{2max} reported a total training session duration of 30-45 min and an intervention duration of 16-30 sessions. In 1 of those studies,[28] the control group performed low-intensity continuous exercise, whereas in 2,[26,27] the control group underwent cycle ergometer training using parameters that were very close to those used in the intervention group. Although those studies found no differences between the intervention and control groups, 1 of the studies[26] reported a trend toward the superiority of the HIIT group over the control group (low-intensity exercise).

None of the included studies evaluated 6MWD, ankle-brachial index, Borg dyspnea scores, or SpO_2. Only 1 study[29] evaluated endothelial function, and the authors found that there were no intragroup or intergroup differences in this variable.

Only 1 study[29] evaluated systolic and diastolic blood pressures and found that there were no pre- or post-intervention differences within the groups and no differences between the groups. Two studies[24,29] evaluated HR, and 1 of the studies[29] found significantly reduced resting HR in both groups ($p < 0.05$); however, there were no differences between the groups. In 1

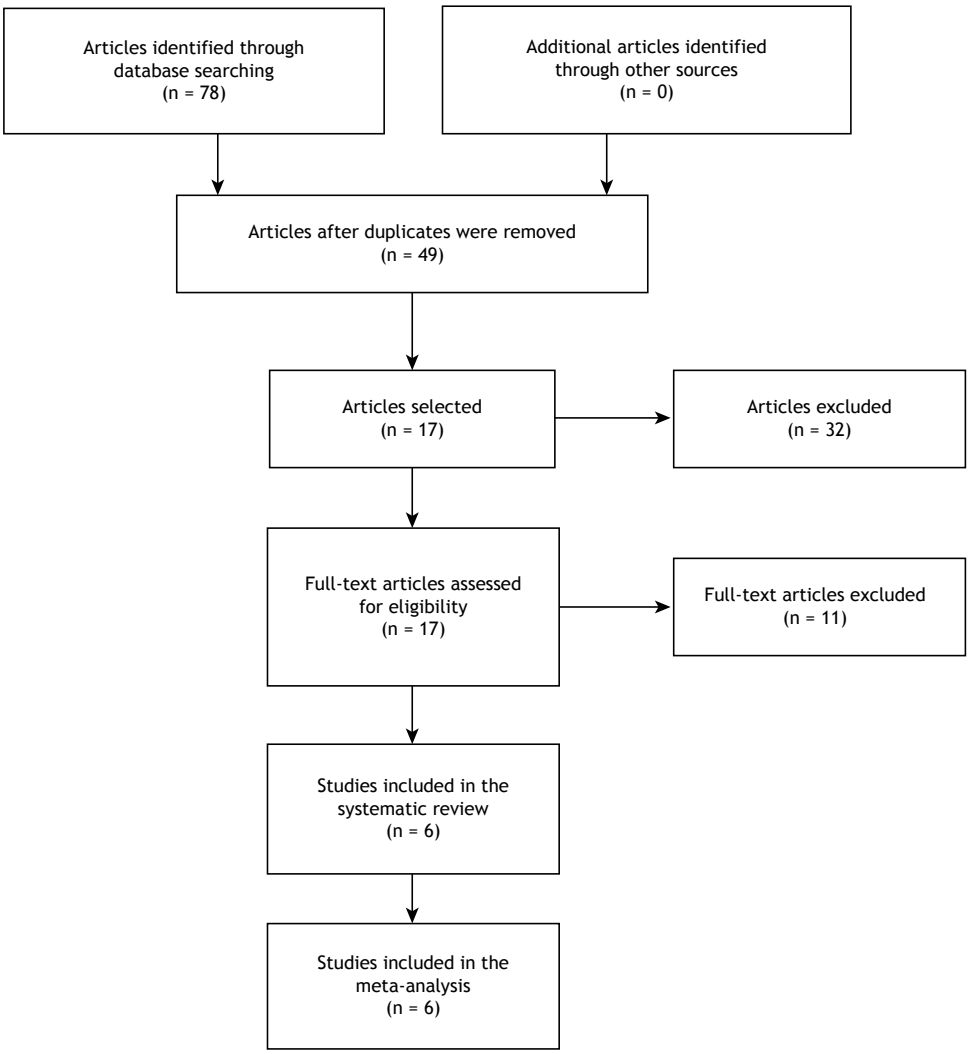

Figure 1. Study inclusion flow chart. RCT: randomized controlled trial; and HIIT: high-intensity interval training.

study,[24] there was an increase in HR in the intervention group ($p < 0.01$), but there were no differences between the groups.

One of the studies[24] evaluated RR and found that there was an increase in RR in the intervention group ($p < 0.05$); however, there was no difference between the groups. The same study[24] evaluated Borg leg fatigue scores and found a decrease in scores in the intervention group ($p < 0.01$), but there were no differences between the groups.

DISCUSSION

The findings of the present study indicate that the effects of HIIT are comparable to those of continuous exercise or any other control intervention regarding relative VO_{2max}, absolute VO_{2max}, and cardiovascular variables in patients with COPD.

In relation to the type and intensity of exercise that should be included in a pulmonary rehabilitation program, studies have shown positive effects of both HIIT and moderate-intensity continuous exercise in patients with COPD.[30,31] In addition, one study[20] comparing continuous and interval training in patients with COPD indicated that the physiological effects of the two types of training are similar in these patients.

A clinical trial[32] showed a reduction in perceived dyspnea, an increase in exercise capacity as measured by VO_{2max}, and an improvement in quality of life in patients with COPD who underwent both low- and high-intensity exercise training. One systematic review[33] showed that interval and continuous exercise both resulted in improved exercise capacity as measured by 6MWD and in improved quality of life. One study[34] comparing different intensities of exercise showed that continuous and interval exercise both appear to be equally effective in improving 6MWD, symptoms, and quality of life in patients with COPD.

In contrast to the results obtained here, studies[17,35,36] evaluating the physiological effects of exercise training appear to indicate that these effects are more beneficial in patients who are able to perform higher-intensity

Table 1. Characteristics of the included studies.

Authors	Intervention group parameters	Intervention duration	Control group parameters	I/C patients, n	I/C patient age, years; mean ± SD
Arnardóttir et al.[25]	Type of training: cycling; exercise intensity: 3-min intervals at ≥ 80% of baseline peak exercise capacity and 3-min intervals at 30-40% of baseline peak exercise capacity; total time: 39 min	16 weeks (2 times a week)	Type of training: cycling (endurance training at ≥ 65% of baseline peak exercise capacity) + breathing and relaxation exercises	28/32	65 ± 7/64 ± 8
Brønstad et al.[29]	Type of training: treadmill; intensity: 4 × 4-min intervals at 90-95% of HR_{max} (10-min warm-up at 50%-60% of VO_{2max} and at 60-70% of HR_{max}); each interval was separated by 3 min of active rest at 50-70% of HR_{max}; total exercise time: 38 min	10 weeks (3 times a week); at least 26 of 32 sessions	Type of training: treadmill; intensity: 70% of HR_{max} (moderate-intensity continuous exercise); total exercise time: 47 min	10/7	65 ± 7/65 ± 5
Hentschel et al.[24]	Type of training: cycle ergometer; intensity: training load = power at the anaerobic threshold + 40% of the difference to peak exercise; total exercise time: 40 min	4 weeks (at least 22 sessions)	Type of training: rehabilitation, education, medications, nutrition, physical therapy, and breathing exercises	84/39	48 ± 10/49 ± 12
Normandin et al.[28]	Type of training: treadmill and cycle ergometer; intensity: 80% of maximum workload (2 min of warm-up and cool-down time not counted); total exercise time: 30 min; intensity increased if Borg = 4 and intensity decreased if Borg = 7 or if HR close to maximum	8 weeks (2 times a week); 16 sessions	Type of training: classroom exercises/calisthenics with 8-10 repetitions (45-60 s; low-intensity continuous exercise); total exercise time: 40 min; total class time: 45 min	20/20	69 ± 7/67 ± 9
Vogiatzis et al.[26]	Type of training: cycling; intensity: 100% of baseline peak work rate (30 s) and 45% of baseline peak work rate (30 s) in weeks 1-4; 120% of baseline peak work rate in weeks 5-8; and 140% of baseline peak work rate in weeks 9-12; total exercise time: 40 min	12 weeks (2 times a week)	Type of training: cycle ergometer exercise at 50%, 60%, and 70% of baseline peak work rate + education, breathing exercises, psychological support, and relaxation	18/18	67 ± 2/69 ± 2
Vogiatzis et al.[27]	Type of training: cycling; intensity: 100% of baseline peak work rate (30 s) and 45% of baseline peak work rate (30 s); total exercise time: 45 min	10 weeks (3 times a week)	Type of training: cycle ergometer exercise at 60%, 70%, and 80% of baseline peak work rate + education, breathing exercises, psychological support, and relaxation	10/9	64 ± 3/67 ± 2

I/C: intervention/control; and VO_{2max}: maximal oxygen consumption.

Table 2. Evaluation of risk of bias.

Study, year	Random sequence generation	Allocation concealment	Blinding of outcome assessors	Reporting of losses and exclusions	Intention-to-treat analysis
Arnardóttir et al.[25]	Yes	No data	No data	Yes	No
Brønstad et al.[29]	Yes	Yes	No data	Yes	No data
Hentschel et al.[24]	No data	No data	No data	Yes	No data
Normandin et al.[28]	No data	No data	No data	Yes	No
Vogiatzis et al.[26]	Yes	No data	No data	No	No data
Vogiatzis et al.[27]	Yes	No data	Yes[a]	Yes	No

[a]Yes for threshold setting.

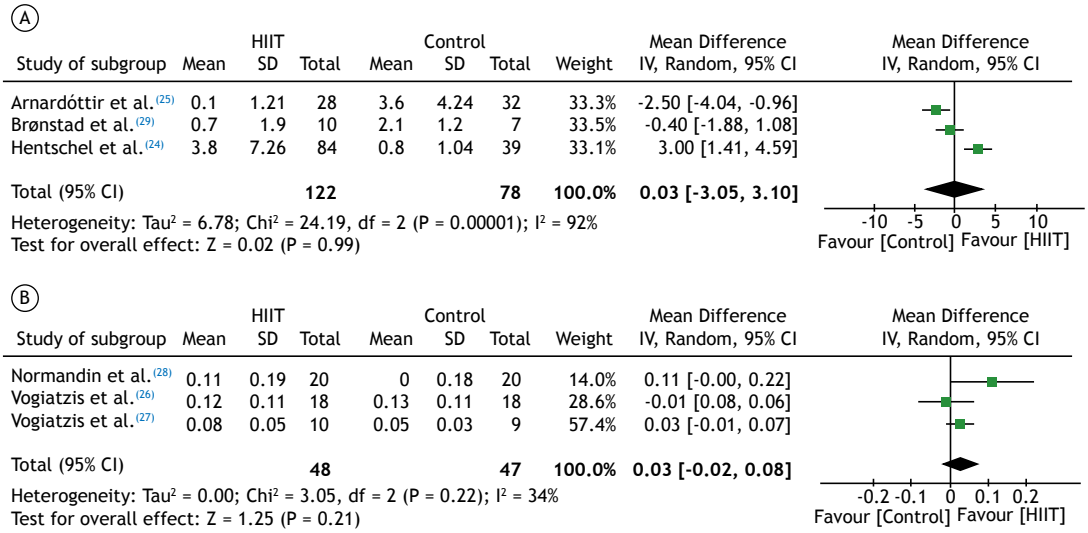

Figure 2. Comparison between the effects of HIIT and those of continuous exercise and rehabilitation on relative VO_{2max} (in A) and absolute VO_{2max} (in B). HIIT: high-intensity interval training; and VO_{2max}: maximal oxygen consumption.

exercise than in those who perform lower-intensity exercise. In addition, a systematic review[37] found a significant increase in maximal exercise capacity as measured by 6MWD and a reduction in leg pain only during interval exercise in patients with COPD. Furthermore, a study[30] evaluating VO_{2max} at different intensities of exercise showed that the response to HIIT was two to three times greater than the response to low-intensity training (85%-95% and 70% of maximal HR, respectively) in healthy individuals.

Hsieh et al.[17] reported that only the patients who were able to perform high-intensity exercise training showed improvements in maximal exercise capacity as measured by VO_{2max} and by 6MWD, in FVC, and in work efficiency. Another study[11] concluded that high-intensity programs tend to result in significant physiological improvements, being especially efficient in increasing exercise capacity and muscle strength.

In general, the optimal intensity of exercise training depends on the individual goals of each patient, and, if the goal is to increase the ability to perform tasks that are above the current level of tolerance, HIIT appears to elicit greater performance increases because it involves significant anaerobic energy utilization and, therefore, can better mimic the physiological requirements of activities of daily living, is tolerable to patients, and can indeed reduce the degree of dyspnea and dynamic hyperinflation through a reduced ventilatory demand.[38]

The formulation of the research problem and the development of eligibility criteria were methodologically rigorous. Study selection was performed by two independent reviewers, who also assessed study methodological quality and agreed on the inclusion and exclusion of studies. The use of meta-analysis increases the robustness of evidence on the influence of HIIT on functional and cardiovascular variables.

We found that most of the studies included in the present review had a high or low risk of bias and that none included all items evaluated. For example, only 1 study reported concealment of allocation and blinding of outcome assessors, characteristics that could have a direct influence on the results. Therefore, it is possible that further studies with higher methodological quality in terms of the variables studied will change current findings. Nevertheless, few randomized controlled trials were found, and most of the studies involving HIIT and patients with COPD are quasi-experimental.

Although we found moderate and high heterogeneity in the meta-analyses of VO_{2max}, probably because of the intervention protocols and the control groups (different intensities of continuous exercise), it was not possible to perform sensitivity analyses because of

the small number of studies included in each analysis, which makes further analyses difficult.

In conclusion, our findings should be interpreted with caution because the included studies have a high risk of bias, especially in terms of concealment of allocation, blinding of outcome assessors, and intention-to-treat analysis. The lack of these methodological characteristics could have a direct influence on the study results.

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Discordance between old and new criteria for stratifying patients with COPD

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TO THE EDITOR:

Medical decisions must be based on accurate patient evaluations and on robust scientific information. The objective of clinical guidelines is to produce useful recommendations by identifying the most relevant scientific information that should be adapted and applied (with caution) in individual patients. This is particularly true in COPD, a highly complex, heterogeneous disorder. The objective of this study was to evaluate how the questionnaires used in symptom evaluation and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD assessment tool can affect COPD classification.

This was a cross-sectional study conducted at the Outpatient Pulmonary Clinic of the *Hospital da Senhora da Oliveira*, in the city of Guimarães, Portugal. We included consecutive patients over 40 years of age who had been diagnosed with COPD according to the GOLD criteria[1] and in whom the disease was stable. The study was approved by the Research Ethics Committees of the *Hospital da Senhora da Oliveira* and of Minho University, in the city of Braga, Portugal, as well as by the Portuguese Data Protection Authority. All participating patients gave written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[2]

We applied a questionnaire designed to collect demographic and clinical data. Symptoms were evaluated with the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) scale (for dyspnea). The number of episodes of acute exacerbation of COPD (AECOPD) in the last year was evaluated. We defined AECOPD in accordance with the GOLD criteria: as an acute worsening of respiratory symptoms that results in the need for additional treatment, as well as prompting an unplanned medical visit. All participants underwent pulmonary function tests in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society,[3,4] and the results were referenced by using the Global Lung Function Initiative predictive equations.[5] Statistical analyses were then performed.

We studied a total of 303 outpatients with COPD. The main demographic, clinical, and functional characteristics of the patients are shown in Table 1. Only 207 patients (68.3%) completed the CAT and mMRC questionnaires. Applying the proposed GOLD cut-off points for degree of dyspnea (mMRC grade) or level of symptom severity that requires regular treatment (CAT score), we found discordance between the two measures in 47 (22.7%) of the 207 patients: 32 (15.5%) were categorized as group A and B; and 15 (7.2%) were categorized as group C and D. In 38 of those patients, the CAT score was ≥ 10 and the mMRC grade was < 2, whereas the other 9 patients presented an mMRC grade ≥ 2 and a CAT score < 10. The distribution of patients and the mean FEV_1 (% of predicted) in each GOLD group, for the two different (2016 and 2017) versions of the GOLD guidelines are also presented in Table 1. When we applied the 2017 GOLD criteria, 74 patients (24.4%) were moved from a higher severity group to a lower severity group.

In the present study, there was significant discordance between the CAT scores and mMRC grades, showing that the impact of COPD goes beyond just dyspnea. Therefore, in the 96 patients who did not complete the CAT, the symptomatic impact might have been undervalued and the proposed treatment might have been significantly different than what they really needed. These observations are consistent with those of other studies.[2] In a study conducted in Spain, the 2011 revision of the GOLD guidelines, which leaves the choice of method for determining the symptomatic impact (mMRC scale or CAT) up to the physician, was evaluated in terms of the comparison between the two measures.[6] The authors found that the classification of COPD patients varied depending on the measure employed, more than 25% of patients being classified in different "horizontal" categories, with different proposed treatments.

The GOLD ABCD assessment tool is currently used in order to guide pharmacological treatment. We observed discordance between the 2016 and 2017 revisions of the GOLD guidelines in 24.4% of the patients in our sample. Many of them, previously classified as belonging in group C or D, were reclassified as belonging in group A or B, for which the proposed pharmacological treatment is significantly different. Our data are corroborated by those of previous studies. One recent study compared the 2011 and 2017 revisions of the GOLD ABCD assessment tool in a sample of 1,532 patients with COPD.[7] The authors found that approximately 47% of the 1,070 patients who were classified in the higher-severity groups when the 2011

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Table 1. Demographic, clinical, and functional characteristics of patients with COPD, together with a comparison between the 2016 and 2017 Global Initiative for Chronic Obstructive Lung Disease criteria in terms of the distribution of patients and mean FEV_1.[a]

Characteristic	(N = 303)
Male gender	241 (79.5)
Age, years	67.5 ± 10.2
Age ≥ 65 years	186 (61.4)
≤ 3 years of schooling	89 (29.4)
Monthly income < €530	197 (65.7)
Smoking history, pack-years	49.3 ± 32.4
mMRC scale grade ≥ 2	185 (61.1)
CAT score ≥ 10	152 (72.4)
≥ 2 episodes of AECOPD in the last year	115 (38.0)
Post-bronchodilator FEV_1, % of predicted	53.2 ± 19.7
GOLD 2016	
Group	
A	51 (16.8)
B	66 (21.8)
C	23 (6.6)
D	163 (53.8)
FEV_1, % of predicted, by group	
A	76.17 ± 14.20
B	65.76 ± 12.81
C	47.01 ± 14.98
D	41.78 ± 19.68
GOLD 2017	
Group	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)
FEV_1, % of predicted, by group	
A	66.67 ± 20.07
B	53.61 ± 17.45
C	59.20 ± 21.75
D	43.40 ± 16.02

[a]Values expressed as mean ± SD or as n (%). mMRC: modified Medical Research Council; CAT: COPD Assessment Test; AECOPD: acute exacerbation of COPD; and GOLD: Global Initiative for Chronic Obstructive Lung Disease.

revision was used were reclassified into lower-severity groups, leading to treatment de-escalation, when the 2017 revision was used. Tudoric et al.[8] compared the 2016 and 2017 GOLD criteria, demonstrating two "vertical" shifts in the distribution of patients with COPD, more than one third of the patients being reclassified from group D to group B when the 2017 criteria were applied.

Medical decisions and pharmacological treatment can be significantly different when distinct validated tools, such as standardized questionnaires and clinical guidelines, are used. The undervaluation of symptoms can result in a greater need for rescue medication, lower quality of life, or lower exercise capacity. Nevertheless, the transition from the 2016 to the 2017 revision of the GOLD ABCD assessment tool would be expected to have a significant effect on therapeutic strategies. The worsening of the prognosis in groups A and B, due to the higher mean airflow limitation, is likely to make any acute exacerbation more serious. For example, the discontinuation of inhaled corticosteroids can be harmful in some of these patients.

Standardized questionnaires, such as the CAT and mMRC, should be used in concert, and the results should be integrated into a detailed clinical history. The changes in the classification of COPD severity in the 2017 revision of the GOLD ABCD assessment tool must be applied with caution to avoid undertreatment.

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Gastric pseudo-obstruction as an initial manifestation of thymoma

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TO THE EDITOR:

Thymomas and thymic carcinomas are rare, accounting for 20% of all mediastinal tumors. They are usually diagnosed as incidental findings on chest imaging performed for another reason or performed because of the presence of mass effect-related symptoms or paraneoplastic syndrome, such as myasthenia gravis. They have similar incidence in men and women and most commonly occur in the 40- to 60-year age group. There are no risk factors.[1,2]

We would like to present the case of a 79-year-old female patient who presented to our facility with a two-month history of weight loss and constipation. She was admitted to the hospital with signs of intestinal obstruction, abdominal bloating, and vomiting. A nasogastric tube drained 3,000 mL of stool-like secretion. Abdominal X-ray and ultrasound revealed a dilated stomach with an air-fluid level (Figures 1A and 1B). Upper gastrointestinal endoscopy revealed no points of mechanical obstruction; there was erosive reflux esophagitis, exuberant gastric dilatation associated with gastric stasis, and hypertrophic pyloric stenosis. Serology for Chagas disease was negative.

The assessment continued with abdominal CT, which showed no evidence of any obstructive factor or tumor, and chest CT, which identified a well-demarcated anterior mediastinal mass with a maximum diameter of approximately 5 cm and no invasion of adjacent structures (Figure 1C). Given the possibility of paraneoplastic syndrome, video-assisted thoracoscopic resection was performed, and pathological examination showed small cell neoplasm of uncertain malignant histogenesis and immunohistochemistry, confirming the diagnosis of type B1 thymoma.

Following tumor resection, the patient experienced a lower frequency of vomiting and was able to tolerate the diet. Gastrography was performed which showed contrast progression and a normal-sized stomach with peristalsis (Figure 1D). A second endoscopy revealed a normal stomach with strong peristaltic waves and no sign of previous hypertrophic pyloric stenosis. The patient was discharged on an oral diet. Serum antibody testing for myasthenia gravis and paraneoplastic syndrome was ordered.

Gastroparesis consists of delayed gastric emptying of solids in the absence of mechanical obstruction. The

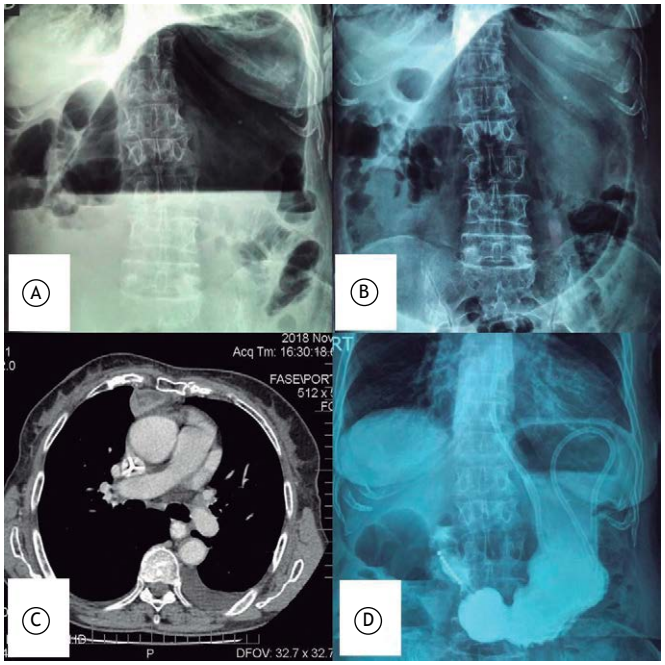

Figure 1. In A and B, abdominal X-ray showing gastric bloating. In C, CT scan showing a well-demarcated anterior mediastinal tumor. In D, gastrography showing normal gastric emptying.

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incidence of gastroparesis is higher in female patients, and survival is significantly lower in this population than in the general population. The most common conditions associated with gastroparesis are functional dyspepsia, in 25%; postoperative states (antrectomy, vagotomy, Roux-en-Y gastric bypass), in 25%; other conditions (scleroderma, anorexia nervosa, uremia, paraneoplastic syndrome), in 15%; and diabetes, in 25%.[3]

In non-diabetic, non-Chagas disease patients with no mechanical obstruction and symptoms of gastroparesis, a diagnosis of paraneoplastic syndrome should be considered. Chief among the tumors to be tested are lung, ovarian, and breast carcinomas, as well as mediastinal tumors, such as neuroendocrine carcinomas and thymoma.[4] Myasthenia gravis is the most common form of thymoma-related paraneoplastic neurological syndrome.

In the context of paraneoplastic syndromes causing gastrointestinal dysmotility, the pathogenesis can be explained by the autoimmune mechanism that affects the intrinsic enteric nervous system (interstitial cells of Cajal and myenteric plexus) and the extrinsic enteric nervous system (autonomic nervous system).[5] Some antineuronal antibodies, such as N-type calcium channel-binding antibodies, acetylcholine receptor antibody, type 1 antineuronal antibody, and anti-CV2 antibody, can be expressed by the tumor.

In patients who experience symptom improvement following tumor resection, the diagnosis can be made regardless of serum levels of those antibodies. In those patients in whom no tumor is found, determining serum levels is more important. The currently recommended treatment consists of resection of the primary tumor, when such a tumor is present, and the use of a selective acetylcholinesterase inhibitor for symptom relief.[5] Preoperative biopsy is indicated in cases of lesions that appear to be malignant or that infiltrate adjacent structures.

Various paraneoplastic syndromes may occur in patients with thymic tumors; however, those syndromes are difficult to diagnose. It is paramount that they be clinically recognized and antibody levels be determined. Studies are needed so that the pathophysiology of those disorders can be understood.

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Should active case finding be conducted among patients with respiratory symptoms independently of local epidemiological settings?

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TO THE EDITOR:

Since the implementation of the directly observed treatment short course (DOTS) strategy by the World Health Organization, it has been recommended that patients presenting with respiratory symptoms (i.e., patients who have had cough and expectoration for three weeks or more) undergo microscopic examination of two sputum smears for early diagnosis of tuberculosis.

According to the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program), the estimated prevalence of individuals with respiratory symptoms is 1% in the general population and 5% among those ≥ 15 years of age seeking treatment at health care facilities (HCFs), the prevalence of active pulmonary tuberculosis among individuals with respiratory symptoms being 4%. According to the World Health Organization, it is estimated that prevalence of respiratory symptoms is 5% at HCFs in developing countries.[1] These rates are related to different epidemiological settings and can therefore vary depending on HCF and local population characteristics.

Many studies have focused on estimating the prevalence of individuals with respiratory symptoms either in the community or among those seeking treatment at HCFs. In the cities of Vitória[2] and Rio de Janeiro,[3] Brazil, the prevalence of individuals with respiratory symptoms among those seeking treatment at HCFs was 4.0% and 10.7%, respectively. In the Federal District of Brasília,[4] Brazil, the prevalence of individuals with respiratory symptoms in the community ranged from 4.8% to 5.7%. Few studies have simultaneously examined the prevalence of individuals with respiratory symptoms in the community and among those seeking treatment at HCFs.

The objective of the present study was to determine the prevalence of individuals with respiratory symptoms and of tuberculosis in the city of Paranaguá, Brazil, where the incidence of tuberculosis is high (i.e., 99/100,000 population). This was a descriptive study involving a population-based survey and a survey of patients seeking treatment at HCFs between September and November of 2010, when the incidence of tuberculosis was 23/100,000 population in the state of Paraná, Brazil and 37/100,000 population in the country as a whole.

Cluster sampling is recommended for population-based studies[5] and was used in the present study in order to obtain a representative sample of the community and of patients treated at HCFs, being weighted by population size and number of visits in the previous year so that neighborhoods that are more populous and HCFs that treat more patients had more clusters. Residents of special census tracts/"subnormal agglomerations" (i.e., slums)[6] were excluded from the population-based (household) survey because the prevalence of respiratory symptoms and tuberculosis in such individuals is known to be high. Individuals seeking treatment at primary care clinics or in the Family Health Program participated in the survey of HCFs, regardless of the reason for seeking treatment. All participants were ≥ 10 years of age and completed a questionnaire on sociodemographic data, duration of cough, and tuberculosis signs and symptoms.

Sample size was calculated by multiplying a simple random sampling formula — $n = Nz^2p(1 - p)/[d^2(N - 1) + z^2p(1 - p)]$ — by the design effect (DE = 2) to correct for differences in sample size (within-cluster correlation).[2,5]

The community sample consisted of 1,020 individuals randomly selected from 30 clusters in the 17 most populous neighborhoods, with approximately 30 individuals in each cluster (p = prevalence of individuals with respiratory symptoms = 1%). An estimated sample of 757 HCF patients were selected from 25 clusters in nine active HCFs (p = 5% of the total number of visits). For both samples, $z^2 = 1.96$ and d = 2%.

Individuals presenting with productive cough were classified as having cough independently of the duration of cough; those with a ≥ 21 day-history of cough were considered to have respiratory symptoms. Patients with bacteriologically confirmed pulmonary tuberculosis were defined as those with positive bacteriological findings, whereas patients with pulmonary tuberculosis not confirmed bacteriologically were defined as those diagnosed with tuberculosis on the basis of clinical and radiological criteria.

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Table 1. Distribution of the sample of individuals in the community and at health care facilities, by type of examination performed, outcome, and duration of productive cough, Paranaguá, Brazil.

Variable	Duration of productive cough, days										95% CI	p*
	1-7		8-14		15-20		≥ 21		Total			
	n	%	n	%	n	%	n	%	n	%		
Community												
AFB smear microscopy, 1st sputum sample												
• Performed	22	48.9	5	62.5	5	62.5	9	32.1	41	43.6	33.4-54.2	0.65
• Not performed	23	51.1	8	37.5	3	37.5	19	67.9	53	56.4	45.8-66.6	
AFB smear microscopy, 2nd sputum sample												
• Performed	21	46.7	5	62.5	5	62.5	9	32.1	40	42.5	32.4-53.2	0.66
• Not performed	24	53.3	8	37.5	8	37.5	19	67.9	54	57.5	46.8-67.6	
AFB culture[a]												
• Performed	16	35.5	4	30.7	3	37.5	5	17.9	28	29.8	20.8-40.1	0.14
• Not performed	29	65.5	9	69.3	5	62.5	23	82.1	66	70.2	59.9-79.2	
Chest X-ray												
• Performed	14	31.1	3	23.0	3	37.5	7	25.0	27	28.8	19.8-39.0	0.39
• Not performed	31	68.9	10	77.0	5	62.5	21	75.0	67	71.2	61.0-80.1	
Outcome												
• No TB (negative smear and culture results; clinical evaluation)	28	62.2	8	61.5	5	37.5	13	46.4	54	57.4	47.8-67.6	0.48
• No TB[b] (home visit, telephone call, reporting systems)	17	37.8	5	38.5	3	62.5	15	53.6	40	42.6	32.4-53.2	
Health care facility												
AFB smear microscopy, 1st sputum sample												
• Performed	16	32.0	1	33.3	3	25.0	7	70.0	27	40.2	28.5-53.0	0.10
• Not performed	34	68.0	2	66.7	1	75.0	3	30.0	40	59.8	47.0-71.5	
AFB smear microscopy, 2nd sputum sample												
• Performed	16	32.0	1	33.3	3	25.0	7	70.0	27	40.2	28.5-53.0	0.10
• Not performed	34	68.0	2	66.7	1	75.0	3	30.0	40	59.8	47.0-71.5	
AFB culture[c]												
• Performed	10	20.0	1	33.3	2	50.0	6	60.0	19	28.3	18.0-40.7	0.47
• Not performed	40	80.0	2	66.7	2	50.0	4	40.0	48	71.7	59.3-82.0	
Chest X-ray[d]												
• Performed	11	20.8	0	0	2	50.0	4	44.5	17	26.1	16.0-38.5	0.25
• Not performed	38	79.2	3	100.0	2	50.0	5	55.5	48	73.9	61.5-84.0	
Outcome												
• Pulmonary TB[e]	1	2.0	0	0	0	0	1	10.0	2	3.0	0.4-10.4	0.68
• No TB (negative smear and culture results; clinical evaluation)	11	22.0	3	100.0	4	100.0	9	90.0	27	40.3	28.5-52.9	
• No TB[f] (home visit, telephone call, reporting systems)	38	76.0	0	0	0	0	0	0	38	56.7	44.0-68.8	

TB: tuberculosis. [a]Of a total of 37 samples, 9 were discarded: insufficient sample, in 5; sample leakage, in 3; and sample contamination, in 1. [b]Two years after the study period, active case finding was conducted among all of the individuals with cough and patients with respiratory symptoms who did not undergo screening during the study period: 15 were asymptomatic; 2 had respiratory symptoms and underwent screening (sputum smear microscopy, sputum culture, and chest X-ray); and 23 were lost to follow-up, official database searches returning no information on TB in those individuals. [c]Of a total of 27 samples, 8 were discarded because they were insufficient. [d]No data on 2, who were therefore excluded from the analysis. [e]Clinical and radiological confirmation (negative smear results), in 1; and bacteriological confirmation (positive AFB culture), in 1. [f]Two years after the study period, active case finding was conducted among all of the individuals with cough and patients with respiratory symptoms who did not undergo screening during the study period: 11 were asymptomatic; and 27 were lost to follow-up, official database searches returning no information on TB in those individuals. *Fisher's exact test.

All of the individuals who presented with cough were instructed to undergo microscopic examination of two sputum smears and AFB culture. Individuals were given a sputum container for collection of spot sputum samples at HCFs and at home. All questionnaire data were double entered into an Epi data database, the program being used in order to validate variables of interest. Two years after the study period, active case finding (i.e., systematic screening for active tuberculosis) was conducted among all of the individuals with cough and patients with respiratory symptoms who did not undergo screening during the study period (Table 1). The chi-square test was used in order to compare the differences between proportions and to verify if they were significant; at frequencies lower than 5, the Fisher's exact test was used. The significance level adopted was 5%, and statistical tests were performed using the statistical package Stata, version 13.0 (StataCorp LP, College Station, TX, USA).

The proportions of screened individuals were low in the community and at HCFs (Table 1). Most of the participants declined to provide a spot sputum sample and failed to return a sample.

Of a total of 94 individuals with cough in the community, 28 were considered to be individuals with respiratory symptoms (prevalence, 2.7%; 95% CI: 1.8-3.9%). Of a total of 67 individuals presenting with cough to HCFs, 10 were considered to be individuals with respiratory symptoms (prevalence, 1.3%; 95% CI: 0.6-2.4%). Tuberculosis was identified in 1 individual with a 5-day history of cough and in 1 individual with respiratory symptoms, the prevalence of tuberculosis among all of the individuals who presented with cough to HCFs therefore being 3%.

The present population-based study sought to fill a gap in the literature by simultaneously examining the prevalence of individuals with respiratory symptoms and of tuberculosis in the community and among those seeking treatment at HCFs. Residents of special census tracts/subnormal agglomerations[6] were excluded in an attempt to minimize selection bias. However, their exclusion and the low proportions of individuals undergoing sputum examination are limitations of the present study because they might have resulted in an underestimation of tuberculosis prevalence.

In the present study, the prevalence of individuals with respiratory symptoms in the community was higher than that detected under the PNCT. Our results are similar to those obtained in India (2.7%),[7] Peru (3.3-3.8%),[8] and in some regions of the Federal District of Brasília (4.8-5.7%),[4] all of which are highly endemic for tuberculosis.

Our population-based survey revealed no cases of tuberculosis, a finding that is consistent with those of studies recommending that active case finding be conducted among individuals with respiratory symptoms at an increased risk of disease rather than among those in the general community. Although active case finding can detect cases of tuberculosis among individuals with respiratory symptoms, it is not cost-effective and therefore should be conducted among homeless people, illicit drug users, prison inmates, immigrants, tuberculosis contacts, people living with HIV/AIDS, and people living in deprived areas, for example.[9,10]

The prevalence of individuals with respiratory symptoms among those seeking treatment at HCFs in the present study was lower than that detected under the PNCT and that found in another study.[1] This might be due to the fact that female patients predominated, and women are known to take better care of their health and seek medical attention more promptly when presenting with cough. The identification of cases of tuberculosis among patients presenting to HCFs with a short history of cough reinforces the importance of investigating cough regardless of its reported duration.[3] It should be borne in mind that the prevalence of individuals with respiratory symptoms and of tuberculosis varies depending on HCF and local population characteristics, among other factors. This should be taken into consideration when planning and monitoring tuberculosis control activities in different settings.

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Pseudomonas aeruginosa colonization in the upper and lower airways of a child with cystic fibrosis: a father's meticulous approach to successful eradication

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TO THE EDITOR:

In cystic fibrosis (CF), an inherited disease, progressive lung destruction, triggered by chronic pulmonary infection with opportunistic pathogens, such as *Pseudomonas aeruginosa*, is the leading cause of premature death. Consequently, there is a strong incentive for early detection and eradication of *P. aeruginosa* infection. Monitoring lower airway (LAW) colonization and using targeted therapy is the current international standard, which is considered to provide better chances to eradicate the pathogen before it changes to a mucoid phenotype and forms biofilms, which then makes eradication nearly impossible. However, eradication of a novel *P. aeruginosa* colonization is challenging, and success rates vary widely (60-90%)[1-3] in divergent protocols consisting of the sole use of inhaled antibiotics, such as tobramycin or colomycin, for periods of about one to six months, or combining oral ciprofloxacin with intravenous antibiotics.

In the last years, the importance of the upper airways (UAW) and the paranasal sinuses for eradication success has been recognized because they are sites for pathogen acquisition, pathogen persistence, LAW contamination, and cross-infection.[4-7] In this context, we implemented routine UAW monitoring by nasal lavage performed every three months as a standard procedure at the CF Center in the University of Jena, in the city of Jena, Germany. Thereby, we previously identified CF patients with primary isolated sinonasal *P. aeruginosa* colonization and we found that identical *P. aeruginosa* strains persisted in the UAW of CF patients after lung transplantation, initially pseudomonas-free transplanted lungs having been colonized with those strains.[8] In addition, we proved that 96% of the detected *P. aeruginosa* strains were genetically identical in both UAW and LAW of CF patients chronically colonized with that pathogen, which underscores the "united airway" concept.[8]

Here, we demonstrate that periodic and close monitoring of LAW and UAW colonization and the use of an aggressive treatment regimen resulted in successful and longstanding eradication of *P. aeruginosa* in a 13-year-old male patient with CF (homozygous F508del genotype). In November of 2011, when the patient was 6 years old, his first *P. aeruginosa* colonization was identified by means of a routine deep throat swab. Subsequently, in accordance with our standard protocol for intermittent colonization, the patient was monthly monitored for UAW colonization (nasal lavage with 10 mL of isotonic saline per nostril) and LAW colonization (deep throat swabs or sputum collection).[8] After detection of the first *P. aeruginosa* colonization, the father of the patient meticulously documented all culture results and treatments and demanded more efficient therapeutic approaches at every new isolation of the pathogen. Knowing the common standards of therapy, we decided to gradually adapt our approach towards an aggressive eradication regimen with oral or intravenous antibiotics together with inhaled antibiotic therapy. The standard procedure with oral ciprofloxacin and inhaled colistin failed to eradicate *P. aeruginosa* from the LAW (Figure 1), and, five months later, the pathogen was detected in the UAW and LAW. Therefore, we extended the therapy by including quarterly i.v. cycles with ceftazidime and tobramycin and permanent treatment with oral azithromycin. The patients also received colistin by nasal nebulization via a pulsating aerosol nebulizer (PARI SINUS™; PARI GmbH, Starnberg, Germany).[9] This approach was proven to deliver aerosols into the paranasal sinuses by a superimposed vibration of 43 Hz, applied during periods of breath holding. In contrast, conventional nebulization through the nose was shown not to deliver relevant amounts of nebulized drugs to the sinuses.[10] With the continued intermittent detection of *P. aeruginosa* in both airway compartments, an off-label eradication regimen, consisting of simultaneous inhaled aztreonam for the UAW and LAW, alternated monthly with inhaled tobramycin, was implemented. Subsequently, after nine positive *P. aeruginosa* cultures from the LAW and three from the UAW, *P. aeruginosa* was eradicated in January of 2013, as confirmed by negative cultures from UAW and LAW samples collected every month thereafter. In addition, IgG antibody titers related to the pathogen (alkaline protease, elastase, and exotoxin A) remained negative, as they had been before and during the detection of *P. aeruginosa* in UAW and LAW, in control samples routinely taken every year. At this writing, the patient has remained free of the colonization for more than 72 months, which allowed the therapeutic burden to be reduced to a minimum.

Our experience has shown that additional routine sampling of UAW can reveal early sinonasal colonization,

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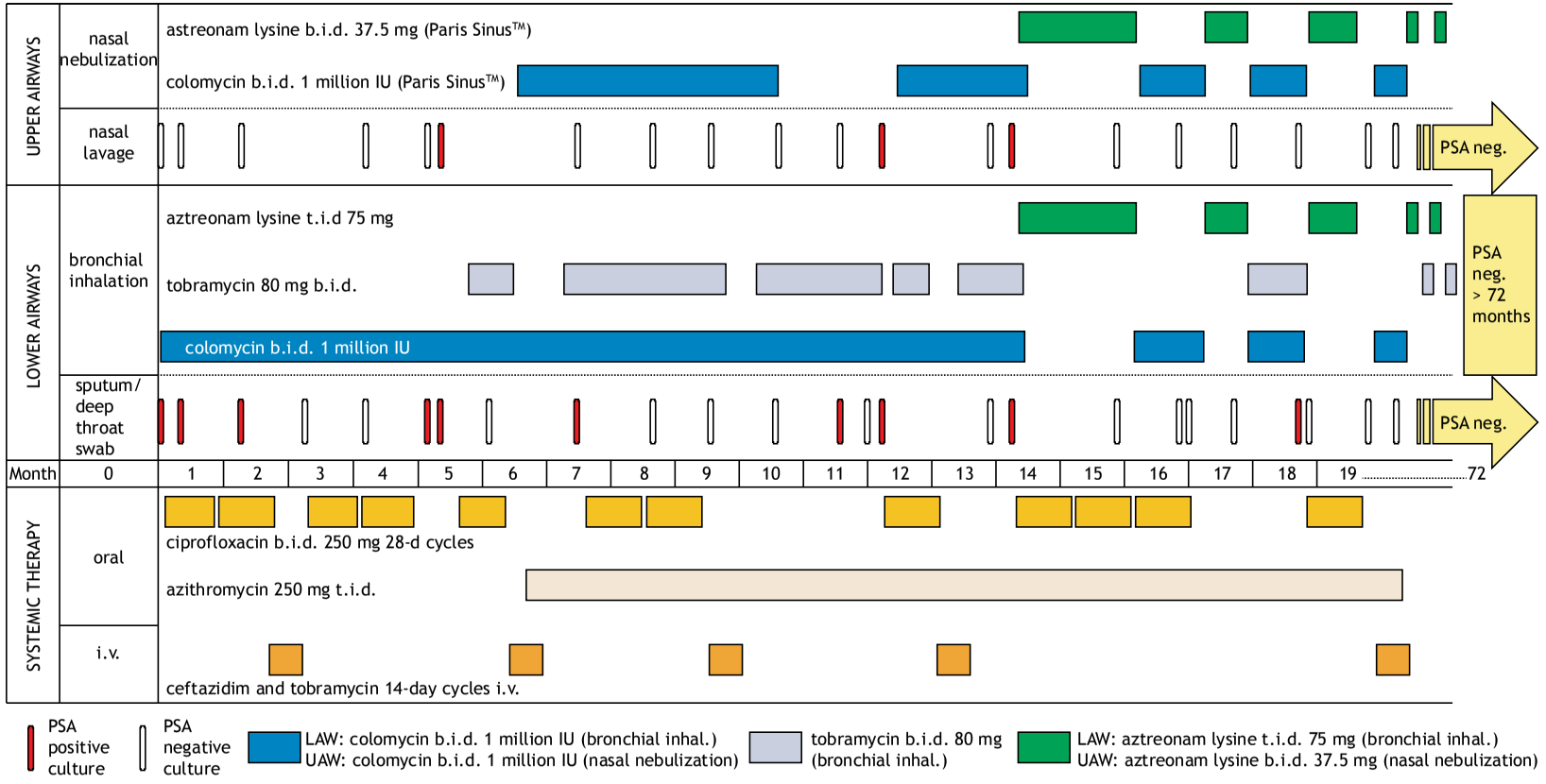

Figure 1. Monitoring of upper and lower airway colonization and therapeutic regimens for *Pseudomonas aeruginosa* (PSA) eradication. b.i.d.: twice a day; t.i.d.: three times a day; neg.: negative; LAW: lower airways; and UAW: upper airways.

which, if unrecognized, most probably would have prevented the successful eradication of the pathogen. Monthly sampling detected intermittent colonization and later confirmed complete elimination of *P. aeruginosa*. Neither would have been possible if we had followed international standards for CF care, which only recommend LAW sampling 2-4 times/year. The use of inhaled antibiotics alone is likely to fail UAW treatment. This corroborates the findings of a group of authors[5] who showed that if *P. aeruginosa* is not eradicated from the entire airway system, it can undergo evolution and diversification processes in order to adapt to the immune system of the host in the paranasal sinuses. If the paranasal sinuses are not considered as a possible reservoir for *P. aeruginosa*, after the cessation of an inhaled therapy alone, the pathogen may descend to the lungs and cause a new pulmonary colonization that can be even more virulent.

No side effects were reported during the off-label eradication regimen. However, the daily burden of treatment widely exceeded the regular number of inhalations in CF patients. Nevertheless, our patient has been free of colonization for 6 years, during which the therapeutic burden could be reduced to a minimum. We show here that the eradication of persistent *P. aeruginosa* is possible with a consistent therapeutic regimen that, in this case, was strongly promoted by the insistence of the family. This may have contributed to a relevantly improved prognosis of the pulmonary function and, thereby, life expectancy of the patient. Based on our experience, we recommend repeated microbiological assessment of both UAW and LAW, especially in patients with intermittent *P. aeruginosa* colonization.[6] Consequently, such an approach should also be included in future studies on *P. aeruginosa* eradication in CF patients.

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Lung ultrasound assessment of response to antibiotic therapy in cystic fibrosis exacerbations: a study of two cases

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TO THE EDITOR:

Cystic fibrosis (CF) pulmonary exacerbations (PEx) cause approximately 50% of the decline in lung function.[1] Although there is no consensus, the criteria for defining PEx currently consist of abnormal sputum and/or chest X-ray findings; anorexia; increased cough; dyspnea; fatigue/lethargy; fever; hemoptysis; decreased overall health status; > 10% decrease in FEV_1; and weight loss.[2] However, two questions remain unanswered[1]: how can we improve the treatment of PEx and which imaging techniques can indicate PEx and/or assess pulmonary involvement? Within this context, we can highlight the use of lung ultrasound (LUS), which is a rapid, radiation-free method that is easily reproducible, widely available, and low cost. LUS can be useful for assessing PEx and response to antibiotic therapy. Experimentally, we used LUS before and after antibiotic therapy in two female CF patients who had PEx. The female CF patients had two sweat chloride results ≥ 60 mEq/L and two pathogenic variants in the *CFTR* gene. The following assessments were performed: completion of a clinical/demographic questionnaire; spirometry; chest HRCT on the day of the first LUS was performed; use of the Bhalla CT scoring system; measurement of SpO_2; LUS; and routine sputum culture (Table 1). This study was approved by the local research ethics committee (CAAE no. 64515817.4.0000.54.04).

According to the international recommendation for point-of-care LUS, this test can detect the presence of A-pattern (normal lung sliding and regular pleural line echogenicity with a predominance of A-line artifacts) or B-pattern (presence of at least three B-line artifacts) per lung region.[3,4] In our study, the lung was divided into 12 regions. The physical and anatomical nature of B-lines ("comet tail" artifacts; hyperechoic, vertical lines that mask A-lines originating from the visceral pleura and move with lung sliding) is not fully understood; however, their occurrence is associated with the presence of hydrostatic and/or inflammatory fluid in the lung interstitium.[4] In addition, LUS can identify consolidation (hypoechoic subpleural area with irregular margins and heterogeneous texture, possibly with a hyperechoic image inside and/or B-lines adjacent to its posterior margin or an aspect similar to that of the liver parenchyma) and pleural effusion (anechoic space between the visceral and parietal pleura).[3]Patient 1 (*CFTR* genotype, F508del/G542X) met the following criteria for PEx: increased cough; increased sputum production and change in sputum appearance/consistency; worsening of findings on pulmonary auscultation; and positive routine culture for *Staphylococcus aureus* and *Achromobacter xylosoxidans*. During follow-up, oral antibiotic therapy was prescribed for 15 days. The Shwachman-Kulczycki (SK) score[5] indicated lack of resistance and end-of-day tiredness, but good school attendance (general activity domain); presence of obstructive pulmonary disease, infection, lobular atelectasis, and bronchiectasis (radiological findings domain); weight and height around the 25th percentile, good muscle mass and tone, and well-formed, near-normal stools (nutrition domain); and no cough, normal heart and respiratory rates, clear lungs, and good posture (physical examination domain). In the assessment of PEx, we considered the patient's or caregiver's report of increased cough, increased sputum production, and/or change in sputum appearance/consistency. However, in the SK score,[5] the presence of cough was assessed during the visit, and this information was different from what was reported previously. In summary, the total SK score was 75, classified as "good". LUS assessment showed that, in four lung regions, the pattern changed from B to A after antibiotic therapy, being classified as a mixed pattern at both time points (Table 1).

Patient 2 (*CFTR* genotype, F508del/F508del) met the following criteria for PEx: increased cough; increased sputum production and change in sputum consistency; tiredness; intolerance to physical exertion; weigh loss; decreased SpO_2; and positive routine culture for mucoid and nonmucoid *Pseudomonas aeruginosa*. During

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follow-up, oral antibiotic therapy was prescribed for 15 days. The SK score[5] indicated lack of resistance and end-of-day tiredness, but good school attendance (general activity domain); presence of obstructive pulmonary disease, infection, lobular atelectasis, and bronchiectasis (radiological findings domain); weight and height below the 3rd percentile, weak muscle tone, reduced muscle mass, mild/moderate abdominal distention, and voluminous, greasy, poorly-formed stools (nutrition domain); frequent cough, usually productive, chest retraction, moderate emphysema, chest deformity, frequent crackles, and digital clubbing (physical examination domain). The total SK score was 45, classified as "moderate". LUS assessment showed that, in one lung region, the pattern changed from B to A after antibiotic therapy, being classified as a mixed pattern at both time points (Table 1).

Both patients were chronically colonized/infected with the aforementioned bacteria and had changes in routine culture results from before to after antibiotic therapy.

The LUS images were examined by a pulmonologist with specific training in LUS interpretation. A second member of the team who specialized in radiology analyzed the LUS findings in a blind fashion. Both professionals scored the LUS images and interpreted the image findings, with identical results. The ultrasound scoring system and the full description of the methods have been published elsewhere.[6]

In reviewing the literature, there is an evident need for a test for assessing antibiotic therapy success in PEx. In addition, there is no consensus regarding the criteria defining the start/end of PEx and the time required for treatment. Furthermore, it is not always possible to identify who will require short-course antibiotic therapy (10-14 days, early responders) or long-course antibiotic therapy (approximately 21 days, late responders).[1,7] Although clinical markers and pulmonary function test results have been used as tools to assess response to treatment, they have limitations and lose specificity as the disease progresses.[1] In this context, our report encourages the applicability of LUS for assessing PEx.

In CF, PEx are markers of disease progression and should be monitored during routine visits. We know that CF patients have experienced an increase in survival despite chronic airway colonization with

Table 1. Data from cystic fibrosis patients and from lung ultrasound assessments before and after antibiotic therapy.

Data	Patient 1		Patient 2	
	Before	After	Before	After
Age, years	22		18	
BMI, kg/m^2	23.34		17.41	
SpO_2	95		92	
Comorbidities	PIns		PIns, DM	
CFTR	F508del/G542X		F508del/F508del	
FVC, % predicted	73	74	38	39
FEV_1, % predicted	55	57	42	41
FEV_1/FVC	75	77	99	94
$FEF_{25-75\%}$,%	24	26	53	46
Bhalla[a]	21		24	
Regions assessed on LUS				
1	A	A	B	A + PI
2	C + PI	C + PI	B + C	B + C
3	B	A	B	B
4	B + PI	B + PI	B	B
5	A + PI	A	B	B
6	B	A	B + C	B + C
7	A	A	B	B
8	B	B	B	B
9	A + PI	A	B + C	B + C
10	B	A	B + PI	B + PI
11	A	A	B	B
12	B	A	B	B
Score[b]	8/36	4/36	18/36	17/36

BMI: body mass index; PIns: pancreatic insufficiency; DM: diabetes mellitus; *CFTR*: cystic fibrosis transmembrane regulator; LUS: lung ultrasound; A: A-pattern; B: B-pattern; PI: pleural irregularity; and C: consolidation. [a]The modified Bhalla CT scoring system was used as in Folescu et al.[10]: the total score for each patient is obtained by summing the scores for each morphological change, which are attributed on the basis of the severity/extent of the abnormality. The total score can range from zero (absence of abnormalities) to 37 (all abnormalities present and severe). [b]The higher the proportion value, the greater the pulmonary involvement in the area, with the presence of consolidation being assigned 2 points and the presence of B-pattern being assigned 1 point. Therefore, the maximum score is 36 points.

bacteria exhibiting increased drug resistance, which culminates in the use of numerous drugs (antibiotics and anti-inflammatory drugs) that require frequent monitoring, since we move toward personalized and precision medicine.[8,9] In this process, LUS could be a tool that accompanies patients in determining their individual response to therapy, without causing complications or exposing patients to radiation.

In summary, LUS could be a useful tool to assess changes due to PEx and response to antibiotic therapy in CF. However, further studies involving a larger sample size are needed in order to confirm our findings, since only one of the two CF patients assessed had distinctly different LUS results before and after antibiotic therapy.

AUTHOR CONTRIBUTION

AOP conceived the project, collected the participant data, and drafted and revised the manuscript; FALM and JDR conceived the study and drafted and revised the manuscript; THS validated the results; and AMAF clinically assessed the study participants and validated the phenotypic findings against reproducibility criteria. All authors read and approved the final version of the article for submission.

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