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Brazilian consensus on non-cystic fibrosis bronchiectasis

Biomarkers in community acquired pneumonia

Chest computed tomography and sleep apnea

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Revaluing the role of the tongue in obstructive sleep apnea

Michel Burihan Cahali[1,2,a]

Since the earliest descriptions of obstructive sleep apnea (OSA), researchers have been struggling to determine the location and pattern of airway collapse in this disease. From the early general notion of upper airway apnea[1] to the most recent detailed classifications of the patterns of collapse seen on drug-induced sleep endoscopy (DISE),[2] understanding the complex mechanical behavior of the upper airway during sleep in individuals with OSA remains a challenge and provides an opportunity to advance the medical and surgical treatment of OSA.

In this issue of the JBP, Passos et al.[3] present the results of multislice computed tomography of the airway in patients with OSA and healthy controls (mean apnea-hypopnea index of 57.1 events/h and 2.2 events/h, respectively) during wakefulness and monitored natural sleep. In the latter case, all control subjects maintained stable breathing during image acquisition, whereas the sleep-state images of the OSA group subjects were acquired during episodes of obstructive apnea or hypopnea, as confirmed by polysomnography. From wakefulness to sleep, there was no significant reduction in the space behind the tongue (retroglossal space) in either group, although there was a significant decrease in the space behind the soft palate (retropalatal space) in the OSA group. The retropalatal space showed a significant reduction in its anteroposterior and lateral dimensions.

To understand the dynamic changes in the airway that lead to obstructive events, Passos et al.[3] evaluated the structures surrounding the pharynx. During sleep, the volume of the lateral pharyngeal wall increased significantly in OSA group subjects and did not change in control group subjects. In sagittal reconstructions, the authors measured the distance from the posterior third of the part of the tongue that lies in front of the soft palate (i.e., the oral tongue) to the posterior pharyngeal wall, which they designated the tongue-pharyngeal distance. Because that distance decreased significantly from wakefulness to sleep in the OSA group subjects, the authors suggested that the retropalatal narrowing is caused by enlargement of the lateral pharyngeal wall associated with the posterior displacement of the upper part of the tongue.

Studies involving imaging of the upper airway during sleep with concurrent polysomnography are still quite rare in the literature.[4] Therefore, Passos et al.[3] are to be commended. The images in their study were obtained during natural sleep rather than by DISE. In addition, the authors were able to quantify the dynamic changes in the pharyngeal lumen and surrounding tissues by computed tomography. This appears to be a nearly perfect setting to study the mechanical behavior of the factors responsible for obstructing the upper airway in OSA. Given the information provided by the authors, the roles played by those factors need to be revalued.

The pharyngeal structures are integrated, consisting of multiple layers of muscle fibers with different origins, insertions, and fusions.[5,6] Ultimately, the change in the shape of the pharynx from the waking state to the sleep state depends on complex interactions among the tissues of the lateral pharyngeal wall, soft palate, and tongue, as well as the non-negligible effect of the jaw opening in the whole scenario.[7] Hence, the levels of obstruction described in DISE examinations do not necessarily represent independent sources of obstruction. For instance, the palatopharyngeus muscle connects the soft palate to the lateral pharyngeal wall and forms the posterior tonsillar pillar, whereas the palatoglossus muscle connects the soft palate to the lateral wall—forming the anterior tonsillar pillar/palatoglossal arch—and extends to the lateral base of the tongue. In fact, the lateral pharyngeal wall is the site of insertion of the soft palate into the pharynx. Not surprisingly, Passos et al.[3] found that, from wakefulness to sleep, lateral pharyngeal wall enlargement correlated significantly with retropositioning of the soft palate in all of the subjects studied.

Passos et al.[3] speculated that, during sleep, the posterior displacement of the tongue would relax the palatoglossal arch and allow the folding and consequent increase in the volume of the lateral wall, as well as pushing the soft palate backwards, all of which, together, cause circumferential narrowing of the retropalatal airway. In that hypothesis, the tongue represents the leading mechanism of obstruction and causes the changes in the other pharyngeal structures. The data presented in the current Passos et al.[3] study are so detailed that we can certainly consider a completely different mechanism. There was absolutely no significant narrowing of the retroglossal space during the obstructive events. In the patients with very severe OSA, among whom the mean body mass index was 34.5 kg/m^2, the base of the tongue moved backward a mean of only 1 mm from wakefulness to obstructed sleep! Because the palatoglossal arch is located precisely in that space, below the level of the soft palate, it seems unlikely that the tongue causes the lateral wall folding, either through relaxation of its interconnections or by directly pushing the lateral wall. The question of whether the oral tongue causes retropalatal collapse is debatable. Among all of the subjects studied, the backward movement of the soft palate from the

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waking state to the sleep state correlated well with that of the oral tongue (r = 0.77), and the thickness of the soft palate did not change significantly in the OSA group, suggesting a synchronized movement of those tissues rather than a push between them. In contrast, the volume of the parapharyngeal fat pad decreased significantly during sleep in the OSA group, likely due to compression caused by the enlargement of the lateral pharyngeal walls.

In conclusion, there is evidence in the Passos et al.[3] study pointing to enlargement of the lateral pharyngeal walls as the leading mechanism of obstruction in OSA, with a direct influence on the positioning of the soft palate and a likely accommodating movement of the upper tongue. On the basis of this alternative proposal, their study helps us understand, mechanistically, why positive airway pressure therapy should be initially applied through a nasal mask rather than an oronasal mask.[8,9] It also helps explain the superiority of surgical techniques that reconstruct the lateral pharyngeal wall over traditional forms of uvulopalatopharyngoplasty.[10] It seems that the key to future advancements in this field is to clarify why the lateral pharyngeal walls enlarge during sleep in individuals with OSA but not in healthy individuals.

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Reasons for smoking or reasons for quitting, that is the question: can administering the Modified Reasons for Smoking Scale make a difference in clinical practice?

Alberto José de Araújo[1,a]

Smoking continues to lead the endless marathon of risk factors that contribute to the occurrence of chronic noncommunicable diseases, being a target for the implementation of the global action plan for the prevention and control of noncommunicable diseases by 2020[1] and of the 2030 Agenda for Sustainable Development,[2] both developed by the World Health Organization.

As the leading cause of preventable disease worldwide, smoking directly accounts for one sixth of all deaths worldwide and kills eight million people every year,[3] 156,000 being in Brazil.[4]

Along with the pressure exerted by the introduction of electronic cigarettes and heated cigarettes, new waves produced by the tobacco industry on the Internet and targeted at adolescents and young adults have led to an unprecedented tobacco epidemic, detected by the Food and Drug Administration in the USA in 2018.[5] This may undermine the efforts of the World Health Organization Framework Convention on Tobacco Control.[6,7]

Despite the excellent results of tobacco control policies in Brazil through a set of measures targeted at preventing smoking initiation and reducing tobacco consumption,[8] there are still 18 million smokers requiring a smoking cessation approach.[9] Brazil is one of the countries that have been pioneers in the provision of smoking cessation treatment via the public health care system, as foreseen in Article 14 of the Framework Convention on Tobacco Control.[7] Scientific evidence has demonstrated that the approach to smokers requires, in addition to cost-effective intervention programs based on behavioral counseling associated with pharmacotherapy,[10] the recognition of physical, emotional, and behavioral factors that favor, condition, stimulate, or maintain nicotine dependence.[11] Among these factors, it is important that the physician considers the smoker's perception of health risks associated with tobacco consumption and the extent to which this perception may influence the smoker's motivation to quit smoking.

In addition to the traditional scale introduced by Karl Fagerström for assessing the level of nicotine dependence, other scales have been tested and validated for assessing the context of factors related to motivation, self-efficacy, levels of anxiety and depression, reasons for smoking, and motivational stages of change.[12]

Training for administering most of these scales is simple, and their administration takes little time during the initial clinical evaluation of smokers and makes it possible to know predictors of and obstacles to smoking prevention, smoking cessation, and maintenance of abstinence, as well as factors that maintain individuals oscillating as to behavioral changes, that is, in a state of ambivalence.[13,14]

In general, smoking is described by many individuals as a means to control their feelings. Tomkins[15] described four basic motivational characteristics of the behavior of smokers: smoking to increase a pleasant/positive affect; smoking to reduce a negative affect; smoking as a habit or without seeking to mitigate/increase any affect; or smoking because of addiction. These characteristics require working with positive and negative affects. On the basis of this model, the Reasons for Smoking Scale (RSS) was created, being originally composed of 23 items and six subscales: manipulation; pleasure; habit/automatism; stimulation; tension reduction/relaxation; and addiction.[16,17]

The Modified Reasons for Smoking Scale (MRSS)[18] consists of 21 questions and seven subscales. The MRSS is a widely accepted scale that provides the opportunity of a more thorough assessment of the smoker and a more detailed psychological profile. In addition, the MRSS is practical to use because it is short, taking only a few minutes to complete.

Different language versions of the MRSS have confirmed its validity and reliability. Berlin et al.[18] tested the French-language version of the MRSS in male and female smokers who participated in a smoking cessation program and had a strong intention to quit. The Dutch-language version of the MRSS was tested in male and female smokers who also had a strong intention to quit.[19] The Brazilian Portuguese-language version of the MRSS was tested by de Souza et al.[20] in male and female blood donors who had no intention to quit smoking.

The MRSS has been used in studies of subgroups of smokers. A longitudinal study of 97 pregnant smokers evaluated the psychological and social factors possibly related to smoking cessation during pregnancy. The most important reason for continuing to smoke was found to be emotional tension reduction, followed by pleasure and addiction.[21] Other studies reported that, although pregnant women were aware of the smoking-related risks to the fetus's health, that awareness was insufficient to motivate them to quit smoking.[22,23] One study suggested that nicotine dependence is the most important health barrier to smoking cessation during pregnancy.[24]

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In this issue of the JBP, Rocha et al.[25] published a cross-sectional, population-based study in which they used the University of São Paulo MRSS, validated for use in Brazil,[26] and evaluated the scale domain scores by demographic variable (gender, socioeconomic class, and level of education), smoking history (pack-years), mood disorder (anxiety and depression), and spirometric diagnosis of COPD.

The study mainly focused on identifying factors involved in tobacco consumption in order to address nicotine dependence prevention and smoking cessation counseling. The authors highlighted the importance of information about the reasons that maintain individuals smoking, which is a relevant distinguishing feature compared with other studies because it helps to develop smoking cessation strategies.

Therefore, knowing and administering the MRSS enables the physician to have a better approach to smoking cessation. This is an extraordinary tool that allows assessment of motives for smoking.

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Biomarkers in community-acquired pneumonia: can we do better by using them correctly?

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INTRODUCTION

Community-acquired pneumonia (CAP) is responsible for a great part of the infectious disease burden worldwide.[1] Although the scientific knowledge on the diagnosis and management of CAP has advanced considerably, there are still gaps and room for improvement. The arrival of biomarkers has generated considerable excitement in the field of medicine, and some biomarkers have been extensively tested in CAP. Herein, we discuss what can be done to move forward in the area, highlighting what we must bear in mind when using biomarkers for clinical purposes and research (Figure 1).

IDEALLY, WHAT DO WE NEED FROM A BIOMARKER IN CAP?

A biomarker is a biological characteristic that is objectively measured and used as an indicator of a physiological process, pathological process or pharmacological response to a therapeutic intervention.[2] Ideally, a biomarker of infection must possess characteristics that facilitate the diagnosis, prognosis, and follow-up. That means that a biomarker should give an indication of the presence of an infection in a rapid and reliable manner, guiding the decision to start antibiotic therapy, always as a complement to the clinical history taking and physical evaluation. In addition, as therapy leads to clinical improvement, the levels of the biomarker should reflect that improvement and should inform decisions regarding the duration of antibiotic therapy. However, persistently altered levels of the biomarker should raise the suspicion of treatment failure or the development of another infectious complication.[3]

In severe infections such as CAP, we need biomarkers that can help us identify patients at a higher risk of a worse outcome, who should be promptly admitted to the hospital or ICU.[1] Although several biomarkers have been studied in CAP, none have been definitively demonstrated to be useful for predicting patient-reported outcomes in CAP.

RECENT ADVANCES IN THE LITERATURE

Most biomarkers are dynamic proteins in the body. Therefore, we cannot interpret a C-reactive protein (CRP) level of 25 mg/L, for example, without considering the starting point ascertained as the onset of infection (i.e., the stimulus for upregulation of the pro-inflammatory biomarker), because, given the CRP dynamic, it could still be low if the stimulus was recent. In fact, it has been reported that, early in the lung infection process (< 3 days after the self-reported symptom onset), CRP levels are lower, whereas procalcitonin levels are higher, than thereafter (≥ 3 days after the self-reported symptom onset). That finding has strong correlation with what is known about the half-life of these biomarkers, as well as their response to stimulus. There is a need for further research in this area, which has direct implications for clinician reasoning in the interpretation of a blood test result.[4] To date, there has been only one study evaluating the influence of time from initial symptoms when validating the initial value of a biomarker for CAP, resulting in limitations on the interpretation of previous studies. Therefore, clinicians have to be careful not to rely on biomarkers alone when deciding whether or not to initiate antibiotic therapy.[1,5]

The use of new molecules or methods for evaluating the inflammatory or immune response in patients with CAP is evolving. In this issue of the JBP, Zhu et al.[6] evaluated two new molecules as prognostic markers in CAP: the NACHT domain-, leucine-rich-repeat- and PYD-containing protein 3 (NLRP3); and the leucine-leucine 37 (LL-37) peptide, a fragment of the cathelicidin protein precursor and an inflammatory regulator. The authors showed that the CAP patients with higher NLRP3 values or lower LL-37 values had higher serum CRP levels and higher white blood cell counts, as well as showing greater severity (as determined by the Pneumonia Severity Index), higher NLRP3 values and lower LL-37 values both being associated with the combination of higher NLRP3 values and lower LL-37 values being associated with higher 30-day mortality in such patients. The authors argued that these could be new targets for CAP treatment.

Another recent finding that has received considerable attention is the incidence of cardiovascular complications after an episode of CAP. In addition, biomarkers traditionally used in cardiology have been applied to CAP. Moving forward in this field, another study in this issue of the JBP, conducted by Akpınar et al.,[7] studied the prognostic value of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) in hospitalized CAP patients without the main factors associated with NT-proBNP increase, such as heart failure, pulmonary hypertension, and acute kidney injury. The authors observed that NT-proBNP levels correlated with the Pneumonia Severity Index and with the mental

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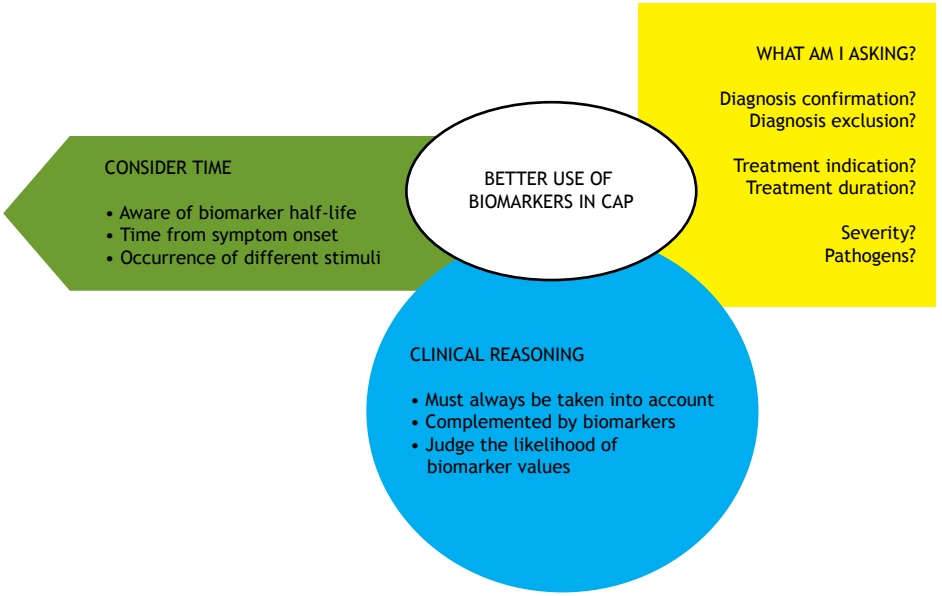

Figure 1. How can we improve the use of biomarkers in clinical practice and research for patients with community-acquired pneumonia (CAP)? Three aspects that clinicians and researchers must always consider when ordering a biomarker test or interpreting its results in a patient with CAP.

Confusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years (CURB-65) score. They also found that, after adjustment for potential confounders in a multivariable analysis, higher NT-proBNP levels were associated with worse outcomes, including ICU admission and 30-day mortality. That novel finding raises the question of where cardiovascular biomarkers could be used in order to predict not only general worse outcomes for CAP but also specific complications, such as cardiovascular events. The prediction of specific events could target the subgroup of patients in need of preventive measures, such as antiplatelet therapy or atherosclerotic plaque stabilization.[7] Specifically, in a baboon model of severe pneumococcal pneumonia, the authors observed direct cardiac damage that could explain the elevation of cardiac biomarkers in CAP.[8]

SHOULD WE RESUSCITATE "OLD" BIOMARKERS?

Because CAP is commonly diagnosed by clinicians, simple, accessible biomarkers are needed. In one recent study,[9] information from complete blood counts was used in order to identify CAP phenotypes and their association with prognosis. For example, red blood cell distribution width has been associated with a poor prognosis and the need for ICU admission in different populations of patients with CAP.[9] In addition, a lymphopenic CAP phenotype, defined as < 724 lymphocytes/mm^3 at diagnosis, has been associated with higher mortality.[10] There is a need for further research on how to implement this knowledge to improve clinical decision-making, as well as on how to incorporate them into prognostic tools, such as the CURB-65 score, in patients with CAP.[11]

In conclusion, we need to use appropriate methods for the clinical application of scores. The normal evaluations by sensitivity, specificity, and ROC curve are not enough. We should use nomograms, analysis of pre- and post-test probabilities, and decision-curve analysis.[12] In addition, repeated measurement of biomarker concentrations, with an assessment of relative variations, before and during antibiotic therapy, could be more informative than is a single value. Therefore, the identification of patterns of response in some biomarkers could help differentiate between favorable and unfavorable clinical courses.[3] This can be helpful for the individualization of the duration of antibiotic therapy or the early identification of patients who are at risk for complications of CAP.

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Pneumomediastinum

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A 23-year-old male patient presented to the emergency room with a complaint of sudden retrosternal pain, which had started two hours prior, accompanied by fatigue. Imaging (Figure 1) showed pneumomediastinum.

Pneumomediastinum, or mediastinal emphysema, is characterized by the presence of air or gas in the mediastinum, and can cause chest pain, dyspnea, soft tissue emphysema, and crackles. Pneumomediastinum is commonly associated with pneumothorax. Air or gas can reach the mediastinum when there is a sudden increase in intra-alveolar pressure resulting in alveolar rupture. The air or gas tracks along the peribronchovascular interstitium and dissects into the hilum, entering the mediastinum. Pneumomediastinum can also result from rupture of the esophagus, trachea, bronchi, or even the neck or the abdominal cavity. In addition, infections in these regions can lead to gas formation.[1,2]

Pneumomediastinum is classified as spontaneous when there is no evidence of trauma, iatrogenic injury, or previous lung disease. The main causes of spontaneous pneumomediastinum are intense physical exercise, the labor of childbirth, pulmonary barotrauma, deep dives, severe paroxysmal coughing, vomiting, and bronchial asthma. Some authors have reported that the main cause of pneumomediastinum of unidentifiable cause is the use of smoked drugs, such as marijuana or crack cocaine. Chest X-ray is the gold standard in the diagnosis of pneumomediastinum. Sometimes, the lateral view facilitates the diagnosis. The most common chest X-ray finding is a thin vertical line, which is lateral and parallel to the mediastinal border, corresponding to the mediastinal pleura separated from the mediastinum by a band of air. This finding is more common on the left. The characteristic CT finding is the presence of gas in the mediastinum, dissecting into anatomical structures (vessels and airways).[1,2]

After careful clinical review, our patient reported having smoked crack before the onset of pain. Barotrauma is a well-known complication resulting from the use of crack, inhaled cocaine, or smoked marijuana. Barotrauma can manifest as pneumothorax, pneumomediastinum, pneumopericardium, or soft tissue emphysema. In cocaine users, an increase in intra-alveolar pressure may occur after smoking, either because of forceful coughing or intentional production of a Valsalva maneuver to increase the absorption and maximize the effect of the drug. When alveoli become overdistended against a closed glottis, they may rupture, and air may dissect into the mediastinum, producing pneumomediastinum.[3] In conclusion, in young individuals, the presence of pneumomediastinum, in the absence of a history of other etiologic factors, should raise the suspicion of crack or marijuana use.

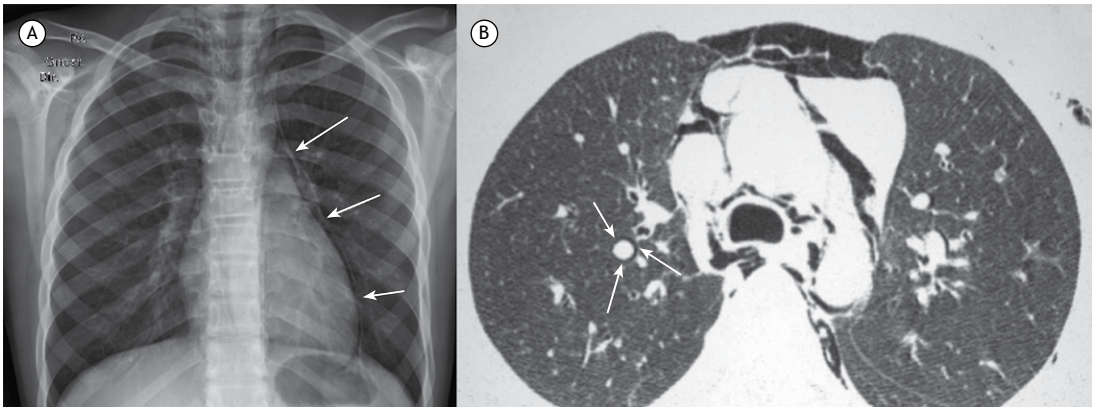

Figure 1. In A, chest X-ray showing a linear opacity parallel to the left mediastinal border, representing the laterally displaced mediastinal pleura separated from the mediastinum by a band of air (arrows). In B, HRCT scan of the chest showing the presence of free gas in the mediastinum, dissecting into anatomical structures (bronchi and vessels). Also note the presence of gas surrounding a pulmonary vessel on the right (arrows).

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Case reports: narratives highlighting clinical experiences that inform practice and future research studies

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PRACTICAL SCENARIO

The authors of a case report[1] describe the success and safety of treating a 65-year-old patient admitted to the hospital with severe COPD and huge emphysematous bullae in the right middle lobe and bronchoscopic lung volume reduction (BLVR). They placed an endobronchial valve in the right middle bronchus after confirming that there was no collateral ventilation.[1] The authors describe the complete treatment regimen given to the patient and report that the huge bullae remained small one week later and disappeared at two months, with the improvement of pulmonary function, symptoms, and quality of life with no signs of obstruction, pneumonia, or pneumothorax. The authors concluded that BLVR may serve as an alternative treatment among selected patients with giant emphysematous bullae.

BACKGROUND

A case report is a comprehensive narrative that provides a clear and detailed description of unique medical experiences with patients that can impact both clinical and research practices. It is very important to publish those experiences, such as in our example, as case reports. Such narratives serve to increase existing knowledge on important clinical topics and to provide insights into new or rare diseases and to nonconventional patient care that can later be more formally evaluated using more sophisticated study designs, such as randomized controlled trials.

In the case report described above,[1] the authors report their experience treating a patient with a specific clinical pattern of COPD with BLVR, because patients with both COPD and giant emphysematous bullae have been excluded from previous treatment studies. The reason for excluding patients with this clinical presentation was that this type of emphysema is a predictor of operative mortality.

We highly recommend that all clinicians, and especially clinician-scientists, take the time to report interesting and unique cases of patients they treat in their home setting that could eventually affect the health of similar patients worldwide. Publishing case reports is an important first step in contributing to answer new questions and guiding informed patient-centered clinical practices. Additionally, for early-stage clinicians, a case report is sometimes the first opportunity to become a published author, since there is no requirement for design or implementation of a clinical research study. Although case reports are at the base of the evidence-based pyramid and are often mistakenly perceived as unimportant in medical science, we highlight that the evidence-based pyramid serves as a guide for clinicians' decision-making processes as a reminder that decisions and recommendations for patients should be based on research data resulting from robust study designs, such as clinical trials, but it does not imply that case reports are not valid.

USING ESTABLISHED GUIDELINES TO PUBLISH CASE REPORTS

To write and publish high-quality case reports, we highly recommend the use of the CARE (CAse REport) Statement and Checklist[2] for the accurate report of information that should be provided in each section of the case report (Table 1).

Table 1. Examples of some of the items on the CARE (CAse REport) Statement and Checklist.[2]

Item	Topic	Checklist Item description
1	Title	Include in the title the name of the study design: "case report".
3a	Abstract Introduction	What is unique about this case? What does it add to the medical literature?
5a	Patient Information	De-identify demographic information and other specific patient information.
9a	Therapeutic Intervention	Describe types of intervention (such as pharmacological, surgical, preventive, and self-care).
10b	Follow-up and outcomes	Provide important follow-up diagnostic/nondiagnostic test results.
11a	Discussion	Discuss the strengths and limitations in your approach to this case.

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Why we should never ignore an "isolated" low lung diffusing capacity

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BACKGROUND

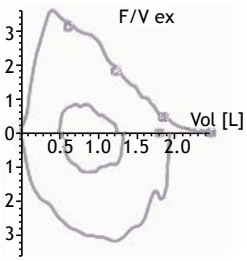
Different diseases causing "opposite" consequences on lung function tests (obstruction vs. restriction) frequently coexist, thereby modifying the pattern that is typical of each disorder. Untangling the underlying physiological disturbances is invariably useful to the pulmonologist.

OVERVIEW

A 72-year-old smoker (80 pack-years) was referred to advanced functional assessment due to "out-of-proportion" dyspnea relative to a normal spirometry performed by her family physician. Our spirometry results were also unremarkable; moreover, lung volumes were within

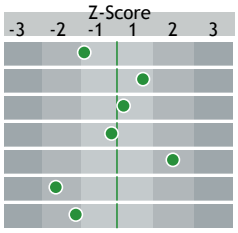
(A) Spirometry

	Pred	Pred LL	Pre	Pre % Pred
FVC	2.19	1.54	2.46	112
FEV_1	1.68	1.19	1.79	106
FEV_1/FVC	78	63	73	94
FEV_1/VC	77.77	63.21	72.87	94
FEF 25-75	1.44	0.61	1.33	93
FEF 50	2.71	2.24	1.83	67
FEF 75	0.31	0.10	0.48	157
PEF	4.85	1.68	3.62	75



Body plethysmography

	Pred	Pred LL	Pred UL	Pre	Pre % Pred
TLC	4.21	3.25	5.17	3.72	88
VC	2.19	1.54	2.87	2.46	112
IC	1.43	0.98	1.89	1.47	103
FRCpl	2.32	1.54	3.09	2.25	97
ERV	0.71	0.48	0.93	0.87	124
RV	1.88	1.25	2.50	1.26	67
RV%TLC	42	30	55	34	80



Lung diffusing capacity

	Pred	Pred LL	Pre	Pre % Pred
DLCO Single...	16.1	12.0	5.0	31
DLCO/VA	4.3	3.2	1.6	37
VA Single...	3.81	3.01	3.19	84

(B)

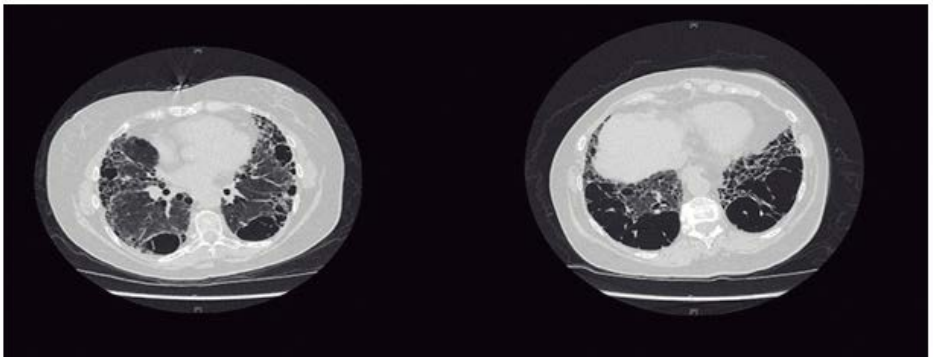


Figure 1. Pulmonary function test results (in A) and high-resolution CT scans of the chest (in B) in a 72-year-old female with "out-of-proportion" dyspnea. Pred: predicted value; Pred LL: lower limit of predicted value; pred UL: upper limit of predicted value; IC: inspiratory capacity; FRCpl: functional residual capacity by plethysmography; ERV: expiratory reserve volume; RV: residual volume; and VA: alveolar volume.

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normal limits with a trend to restriction. Of note, these results contrasted with severely reduced DLCO and carbon monoxide transfer coefficient [K_{CO} = DLCO/alveolar volume (V_A); Figure 1A]. She terminated an incremental exercise test at only 20 W due to severe dyspnea. Despite moderate hypoxemia and hypocapnia, neither hyperinflation nor critical inspiratory constraints were observed.[1] The dead space (V_D)/tidal volume (V_T) ratio was markedly increased at rest (0.60) and during exercise (0.50) in association with severe ventilatory inefficiency (V_E/VCO_2 nadir = 62). HRCT scanning uncovered combined pulmonary fibrosis and emphysema (CPFE; Figure 1B).

Why were spirometry and body plethysmography insensitive to the profound structural abnormalities of the patient? It is apparent that the lung parenchyma with no emphysema was heavily infiltrated by fibrosis (Figure 1B). Thus, opposite mechanical abnormalities canceled out each other, the net result being "normal" flows and volumes. The restrictive abnormalities seem to be physiologically more relevant than the enlarged airspaces—despite the CT scans suggesting otherwise. Notably, low DLCO exposed the ominous effect of both diseases on gas exchange.[2]

Exercise V_E was excessive for metabolic demand because a large fraction of the breath was "wasted" in the V_D, and the patient hyperventilated (low $PaCO_2$).[3] These phenomena might be inter-related: an enlarged V_D/V_T ratio is expected to increase overall (i.e. whole-lung) ventilation; thus, hyperventilation of areas with still preserved ventilation-perfusion would lead to hypocapnia—particularly in the presence of hypoxemia and other sources of increasing chemosensitivity.[4] Of note, V_A was close to TLC (V_A/TLC > 0.80), indicating that the tracing gas used in the single-breath DLCO measurement did gain access to most of the enlarged airspaces seen in Figure 1B.[5] In other words, they were still ventilated but likely not perfused, an important source of "wasted" V_E. Owing to preserved inspiratory capacity, V_T and V_E increased markedly. In contrast, patients with such severe emphysema—but no pulmonary fibrosis—are usually hyperinflated, mechanically constrained, and hypercapnic.[6] Thus, CPFE, paradoxically, gave her a ventilatory mechanical advantage as she could breathe from a "safe" distance from her TLC.[1] Unfortunately, her heightened drive fueled by "wasted" V_E and the vigorous efforts to keep $PaCO_2$ at a low value provoked severe breathlessness.

CLINICAL MESSAGE

Preserved spirometric parameters and lung volumes in symptomatic patients with an interstitial or obstructive lung disease should raise the suspicion of coexistent disorders. An out-of-proportion decrease in DLCO is frequently valuable to expose the severity of functional impairment and track the progression of the underlying diseases.

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State-dependent changes in the upper airway assessed by multidetector CT in healthy individuals and during obstructive events in patients with sleep apnea

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ABSTRACT

Objective: To determine whether airway narrowing during obstructive events occurs predominantly at the retropalatal level and results from dynamic changes in the lateral pharyngeal walls and in tongue position. **Methods:** We evaluated 11 patients with severe obstructive sleep apnea (OSA) and 7 healthy controls without OSA during wakefulness and during natural sleep (documented by full polysomnography). Using fast multidetector CT, we obtained images of the upper airway in the waking and sleep states. **Results:** Upper airway narrowing during sleep was significantly greater at the retropalatal level than at the retroglossal level in the OSA group ($p < 0.001$) and in the control group ($p < 0.05$). The retropalatal airway volume was smaller in the OSA group than in the control group during wakefulness ($p < 0.05$) and decreased significantly from wakefulness to sleep only among the OSA group subjects. Retropalatal pharyngeal narrowing was attributed to reductions in the anteroposterior diameter ($p = 0.001$) and lateral diameter ($p = 0.006$), which correlated with an increase in lateral pharyngeal wall volume ($p = 0.001$) and posterior displacement of the tongue ($p = 0.001$), respectively. Retroglossal pharyngeal narrowing during sleep did not occur in the OSA group subjects. **Conclusions:** In patients with OSA, upper airway narrowing during sleep occurs predominantly at the retropalatal level, affecting the anteroposterior and lateral dimensions, being associated with lateral pharyngeal wall enlargement and posterior tongue displacement.

Keywords: Multidetector computed tomography; Oropharynx; Sleep apnea, obstructive; Polysomnography; Diagnostic imaging; Sleep.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive partial or complete upper airway obstruction during sleep. OSA is common in the general population and can have many consequences, including fragmented sleep, excessive daytime sleepiness, poor quality of life, and poor cardiovascular outcomes.[1-3] The main pathophysiological mechanism in OSA involves changes in the configuration of the upper airway anatomy. The upper airway remains patent during wakefulness but collapses during sleep, when the upper airway muscles relax.[4] Studies using standard imaging modalities, such as X-ray,[5-7] CT,[8-11] and magnetic resonance imaging (MRI),[12-16] to examine the upper airway in patients with OSA have shown that bone and soft tissue characteristics can both increase the risk of OSA. The major risk factor for OSA is obesity, which has been associated with enlargement of the pharyngeal soft tissues, especially the tongue.[11,13] However, the state-dependent behavior of the tongue, soft palate, and lateral walls that leads to upper airway obstruction in patients with OSA is poorly understood.

Pharyngeal obstruction can be visualized directly through drug-induced sleep endoscopy (DISE).[17] However, DISE has some technical limitations: it is invasive and does not allow precise measurements, because of image distortion and the lack of clear anatomical landmarks. More importantly, observation of the pharyngeal lumen during endoscopy provides no insights regarding the surrounding structures. Similarly, MRI of the upper airway during sleep provides limited information because of the technical difficulties involved in monitoring patients and acquiring images during sleep.[18-21] Multidetector CT uses relatively low doses of radiation, allows fast acquisition, and produces high quality three-dimensional (3D) reconstructions of the upper airway. A limited number of studies, involving small samples of subjects, have used CT and MRI to examine the upper airway during sleep.[20-24] Such studies have suggested that the primary site of upper airway obstruction is in the retropalatal region. An even smaller number of studies have characterized the state-dependent pattern of airway collapse.[18,20,24]

The primary purpose of the present study was to document the state-dependent behavior of the structures surrounding the pharynx during upper airway obstruction, using multidetector CT, during well-documented natural sleep in patients with OSA and healthy controls. We hypothesized that airway narrowing occurs predominantly

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in the retropalatal region and results from dynamic changes in the lateral pharyngeal walls and tongue position.

METHODS

Subjects

Male patients with a recent diagnosis of severe OSA, defined as an apnea-hypopnea index (AHI) ≥ 30 events/h, were recruited for the study. Patients with a body mass index (BMI) ≥ 35 kg/m^2 were excluded, as were those with congestive heart failure, neuromuscular disease, coronary artery disease, or a history of stroke. As a control group, healthy male subjects were recruited from among the hospital staff. From the control group, we excluded subjects who reported snoring, subjects who were using any medication, and subjects with an AHI > 5 events/h (Table 1). The local research ethics committee approved the study, and all participants gave written informed consent.

Sleep evaluation

All of the patients in the OSA group were evaluated by full polysomnography on a digital system (EMBLA; Flaga Medical Devices, Reykjavík, Iceland) with the following parameters[25]: electroencephalography (electrodes C3/A2, C4/A1, O1/A2, and O2/A1); electrooculography; electromyography of the submental and anterior tibialis muscles; snoring, identified with a snoring sensor; air flow, as measured with oronasal thermistor and nasal pressure cannula; chest and abdominal wall movements, identified with thoracic and abdominal belts, respectively; electrocardiography; sleep position, determined with a body position detector; oxygen saturation; and heart rate. Among the healthy (control group) subjects, the absence of OSA was confirmed with a type III portable home monitor, which assessed nasal flow (with a nasal pressure cannula), thoracic/abdominal movement, pulse oximetry, and body position (Stardust; Philips Respironics, Murrysville, PA, USA). All sleep studies were scored manually by the same experienced technician, who was blinded to the clinical status of the subjects. An episode of apnea was defined as a ≥ 90% reduction in flow amplitude for at least 10 s. An episode of hypopnea was defined as a ≥ 50% reduction in flow amplitude, accompanied by ≥ 3% oxygen desaturation or a ≥ 10 s awakening.[26]

Study design

Subjects were instructed to restrict their sleep to less than 4 h on the night previous to the CT study and to arrive at the radiology department in the early afternoon after a light meal, having consumed no caffeinated beverages or alcohol on the day of the study, and wearing comfortable clothes. During the CT scans, all subjects were monitored with the same equipment and electrodes used in the full polysomnography, with the exception of the submental and anterior tibialis muscle electromyography electrodes, which were not employed. The polysomnography signals were continuously displayed in the CT control room on a dedicated laptop computer. The CT scanning table was outfitted with a customized mattress and arm supports. Images of the upper airway were initially obtained during wakefulness. The subjects were then instructed to close their eyes and relax. The lights were then turned off. The second series of CT images was acquired after at least 2 min of stable (stage 1 or 2) sleep, during stable breathing in controls and during respiratory events in patients with OSA. A time stamp was issued to the polysomnography acquisition system when the CT scanner was triggered.

CT imaging

The upper airway was imaged in a 16-slice multidetector CT scanner (IDT 16; Philips Medical Systems, Best, The Netherlands). During the CT study, subjects were placed in the supine position, their head being fixed to the scanner head rest with adhesive tape. Images were acquired from the level of the hard palate to the level of the hypopharynx. The following parameters were used: collimation, 1.5 mm; interslice gap, 1 mm; voltage, 120 kV; current, 140 mAs; and rotation time, 1 s.

Anatomical measurements

Axial and sagittal 3D reconstructions were performed to allow linear measurements using an Extended Brilliance Workspace (Philips Medical Systems). As previously described,[18,27] the retropalatal region was defined as that ranging from the hard palate to the tip of the uvula, and the retroglossal region was defined as that ranging from the tip of the uvula to one slice above the epiglottis. Sagittal reconstructions were used in order to measure the length and width of the soft palate, as well as to determine the distance from the edge of

Table 1. Demographic characteristics of the study participants.[a]

Characteristic	Group	
	Control (n = 7)	OSA (n = 11)
Age, years	30.3 ± 4.2	57.7 ± 14.6
BMI, kg/m^2	27.7 ± 2.6	34.5 ± 5.7
Neck circumference, cm	42 ± 1.7	45.6 ± 4.2
AHI, events/h	2.2 ± 1.2	57.1 ± 19.5
Lowest oxygen saturation, %	89 ± 2.3	67 ± 10.6

OSA: obstructive sleep apnea; BMI: body mass index; and AHI: apnea-hypopnea index. [a]Results expressed as mean ± SD.

the posterior third of the oral tongue and the posterior pharyngeal wall, designated the tongue-pharyngeal distance and measured at the level of the superior border of the C2 vertebral body (Figures 1 and 2). The limits of the lateral pharyngeal walls and tongue were defined by manually tracing their contours on each axial image (Figure 1). Volumetric reconstructions of the lateral pharyngeal walls and tongue were performed. Tongue volume was not determined during sleep, because airway narrowing, together with apposition between the soft palate and the tongue, precluded definition of the borders between the soft palate and the tongue. The lateral pharyngeal walls are delimited medially by air and laterally by the parapharyngeal space, which has a lower attenuation due to fat. The anterior border is defined by the anterior contour of the palatine tonsil and follows a diagonal line parallel to the anterior border of medial pterygoid muscle in a caudal direction towards the glossotonsillar sulcus. The upper landmark is the hard palate, and the lower landmark is the tip of the free margin of the epiglottis (Figures 1 and 2). Linear and area measurements were obtained at the narrowest point of the upper airway, at the retropalatal and retroglossal levels (Figure 1). Upper airway volume was quantified through the use of a segmentation technique based on a fixed threshold characteristic of air (−1024 HU to −800 HU) and was assessed for the retropalatal and retroglossal regions. To determine the level of intraobserver agreement, lateral pharyngeal wall volume was measured twice in each of 5 OSA group subjects.

Statistical analysis

Data were analyzed using the Statistical Analysis System, version 9.2 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as means and standard deviations or as medians and interquartile ranges. A general linear model for repeated measures was used in order to compare upper airway measurements among patients and controls during wakefulness and during sleep. Pearson's correlation coefficient was used in order to determine whether the state-dependent changes in the tongue-pharyngeal distance were associated with the dimensions of the retropalatal region and lateral pharyngeal wall. A paired t-test was used in order to compare the

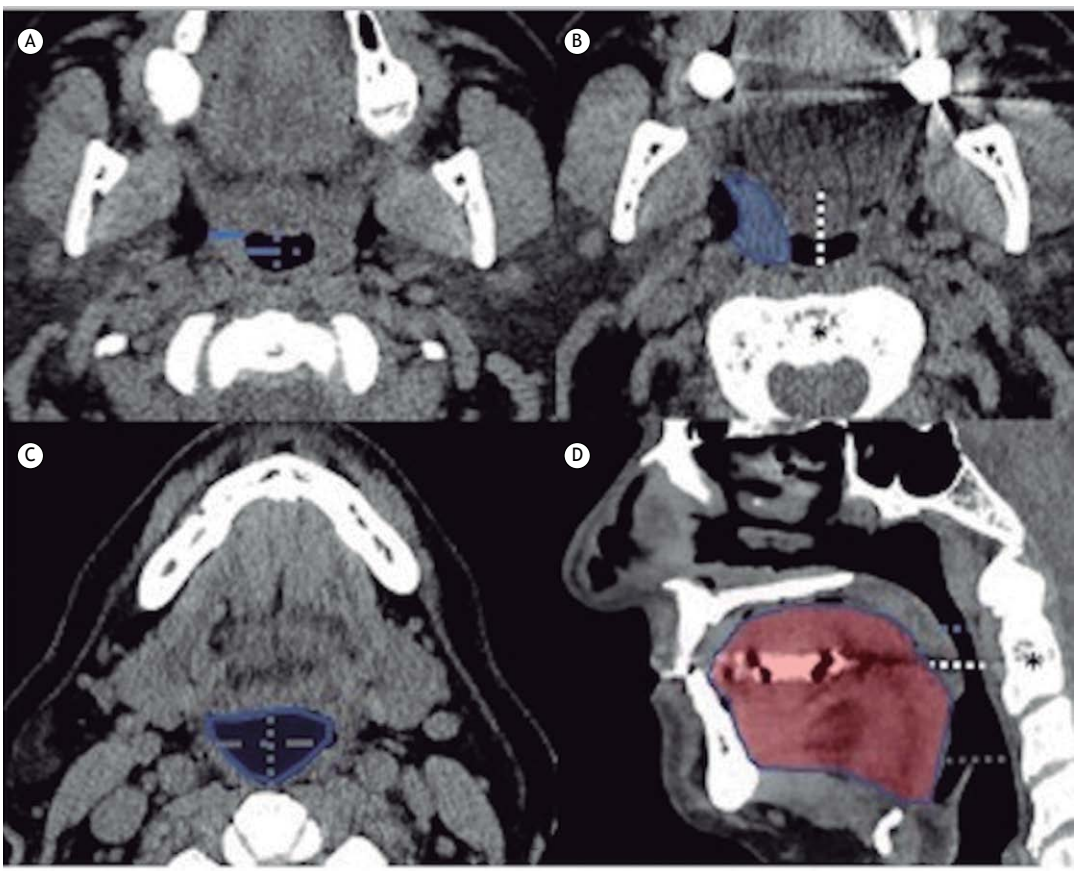

Figure 1. Representative axial and sagittal CT reconstructions of the pharynx during wakefulness in a patient with obstructive sleep apnea. Retropalatal region (A), at the level of the superior border of the C2 vertebral body (* in B), and retroglossal region (C). Contour of the lateral wall (blue outline in B) and lateral wall thickness (solid line in A); anteroposterior diameter of the pharynx (dotted lines in A, C, and D) and lateral diameter of the pharynx (dashed line in A and C); tongue-pharyngeal distance (white dotted line in D); retroglossal area (solid contour in C) and tongue delimitation (red area in D).

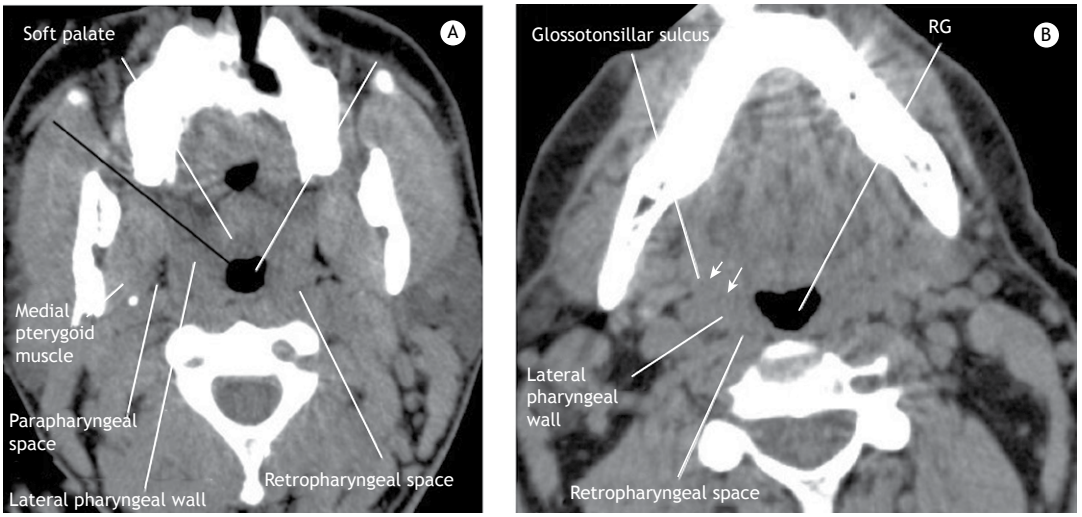

Figure 2. Axial CT images of the retropalatal (RP) and retroglossal (RG) regions (A and B, respectively). The lateral pharyngeal walls are delimited medially by air. The black line in A represents the anterior aspect of the medial border of the lateral pharyngeal wall. The glossotonsillar sulcus (arrows) marks the anterior limit of the lateral pharyngeal wall at the RG level (B). The lateral pharyngeal wall is delimited laterally by the parapharyngeal space and posteriorly by the retropharyngeal space.

waking and sleep states in terms of the retropalatal and retroglossal airway volumes. An unpaired t-test was used in order to compare the patients who were included in the study with those who were excluded. Using a two-way mixed-effects model, we calculated intraclass correlation coefficients in order to determine the level of intraobserver agreement for lateral wall volume measurements. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

A total of 29 male subjects were enrolled in this study (11 healthy controls and 18 patients with OSA). A total of 11 subjects (4 control group subjects and 7 OSA group subjects) failed to fall asleep during the CT examination and were excluded. Therefore, the final sample comprised 18 subjects (7 in the control group and 11 in the OSA group). During wakefulness, no significant differences were observed between the patients with OSA who were included and those who were excluded in terms of the CT variables evaluated. However, there were differences between the control and OSA groups in terms of the mean values for age (58 ± 15 years vs. 30 ± 4 years), BMI (34 ± 6 kg/m^2 vs. 28 ± 3 kg/m^2), AHI (2 ± 1 events/h vs. 57 ± 19 events/h), and lowest oxygen saturation (67 ± 10% vs. 89 ± 2%), all of which were statistically significant ($p < 0.05$ for all).

The duration of each CT acquisition was 4-6 s. The time from CT acquisition during wakefulness to CT acquisition during sleep was 5-90 min. All sleep-state CT scans were acquired during stable breathing in the control group subjects and during obstructive respiratory events, characterized by episodes of hypopnea (n = 4) or apnea (n = 7), in the OSA group subjects.

Representative examples of 3D reconstructions of the upper airway and lateral pharyngeal walls during wakefulness and sleep in a control group subject and in an OSA group subject are shown in Figure 3. The mean tongue volume during wakefulness was significantly greater in the OSA group than in the control group (14.9 ± 2.4 cm^3 vs. 11.4 ± 1.1 cm^3; $p < 0.001$).

Linear and volumetric measurements of the upper airway in the waking and sleep states, in the control and OSA groups, are shown in Table 2. In both groups, upper airway narrowing from wakefulness to sleep was more pronounced at the retropalatal level than at the retroglossal level. In addition, the mean change in airway volume from wakefulness to sleep differed significantly between the retropalatal and retroglossal regions in the OSA group (−45.0 ± 21.3% vs. 16.9 ± 38.5%; $p < 0.001$) and in the control group (−10.8 ± 17.1% vs. 3.0 ± 12.3%; $p = 0.016$). As can also be seen in Table 2, there were trends toward state-dependent reductions (from wakefulness to sleep) in the mean dimensions of the retropalatal region in the control group: anteroposterior diameter ($p = 0.118$); lateral diameter ($p = 0.120$); and airway volume ($p = 0.129$).

In the OSA group, the cross-sectional area of the retropalatal airway decreased from 0.73 ± 0.40 cm^2 in the waking state to 0.19 ± 0.17 cm^2 in the sleep state ($p < 0.001$). Also within the retropalatal airway (Table 2), the OSA group subjects showed similar state-dependent reductions (from wakefulness to sleep) in the mean anteroposterior diameter (0.71 ± 0.25 cm to 0.46 ± 0.28 cm; $p < 0.001$) and mean lateral diameter (1.18 ± 0.49 cm to 0.74 ± 0.54 cm; $p = 0.006$). As can be seen in Figure 4, there was also a reduction in the mean retropalatal airway volume in the OSA group, in which it decreased from 2.64 ± 1.00 cm^3 during wakefulness to 1.39 ± 0.72 cm^3 during

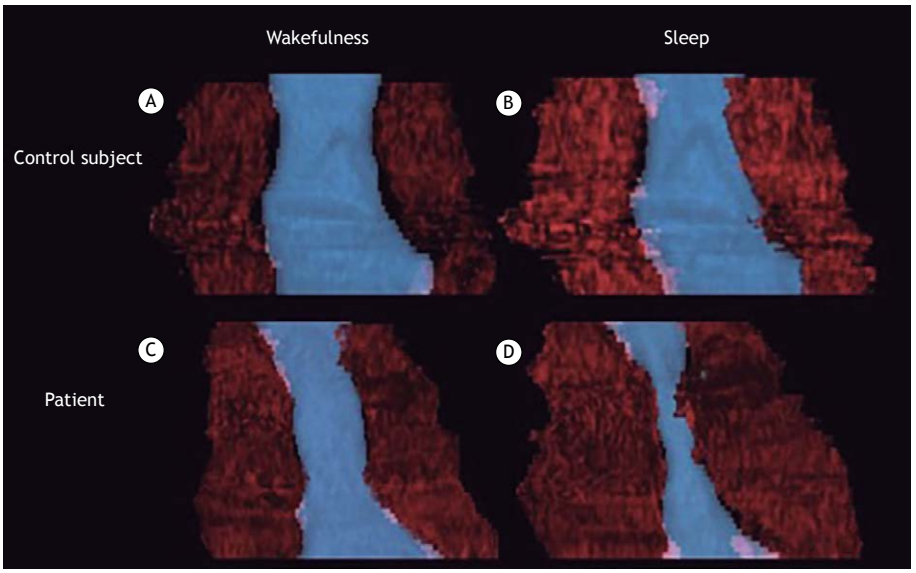

Figure 3. Three-dimensional reconstructions of the upper airway of a representative control subject (A and B) and of a patient with obstructive sleep apnea (OSA; C and D). The lateral pharyngeal walls (in red) and the airway lumen (in blue) during wakefulness (A and C) and sleep (B and D). From wakefulness to sleep, the lateral walls and airway lumen remained unchanged in the control subject, whereas there was widening of the lateral pharyngeal walls and narrowing of the airway lumen in the patient with OSA.

Table 2. Linear and volumetric measurements of soft tissue and airway spaces in waking and sleep states.

Parameter	Group						p†
	Control (n = 7)			OSA (n = 11)			
	Waking	Sleep	p*	Waking	Sleep	p*	
Retropalatal space							
Anteroposterior diameter, cm	0.76 ± 0.14	0.81 ± 0.20	0.118	0.71 ± 0.25	0.46 ± 0.28	0.001	0.001
Lateral diameter, cm	1.76 ± 0.30	1.31 ± 0.65	0.128	1.18 ± 0.49	0.74 ± 0.54	0.006	0.398
Area, cm^2	1.18 ± 0.25	1.08 ± 0.43	0.399	0.73 ± 0.40	0.19 ± 0.17	0.001	0.001
Lateral wall thickness, cm	1.24 ± 0.31	1.28 ± 0.26	0.534	1.53 ± 0.38	1.67 ± 0.41	0.193	0.890
Lateral wall volume, cm^3	11.5 ± 3.1	11.3 ± 3.2	0.878	15.8 ± 6.3	20.1 ± 8.9	0.001	0.010
Soft palate thickness, cm	0.91 ± 0.20	0.91 ± 0.20	1	1.20 ± 0.25	1.10 ± 0.21	0.340	0.443
Soft palate length, cm	3.39 ± 0.27	3.36 ± 0.26	0.356	4.40 ± 0.69	4.50 ± 0.56	0.341	0.484
TP distance, cm	1.58 ± 0.41	1.56 ± 0.47	0.898	1.89 ± 0.28	1.62 ± 0.32	0.001	0.035
Fat pad volume, cm^3	1.60 ± 0.87	1.65 ± 0.81	0.916	3.15 ± 2.30	2.08 ± 1.74	0.006	0.900
Airway volume, cm^3	3.19 ± 0.97	2.82 ± 0.94	0.129	2.64 ± 1.00	1.39 ± 0.72	0.001	0.003
Tongue volume, cm^3	11.4 ± 1.10	----	----	14.9 ± 2.40	----	----	----
Retroglossal space							
Anteroposterior diameter, cm	1.36 ± 0.45	1.40 ± 0.45	0.761	1.63 ± 0.46	1.53 ± 0.70	0.284	0.186
Lateral diameter, cm	2.56 ± 0.32	2.53 ± 0.94	0.899	2.36 ± 0.58	2.15 ± 0.41	0.242	0.980
Area, cm^2	2.47 ± 0.97	2.57 ± 1.37	0.776	2.52 ± 0.91	1.80 ± 1.50	0.099	0.183
Airway volume, cm^3	3.83 ± 1.78	3.89 ± 1.85	0.623	3.80 ± 1.78	4.64 ± 1.85	0.147	0.485

OSA: obstructive sleep apnea; and TP distance: tongue-pharyngeal distance (distance from the edge of the posterior third of the oral tongue to the posterior pharyngeal wall).*Waking state vs. sleep state. †Control group vs. OSA group.

sleep ($p < 0.001$), with a consequent increase in the mean volume of the lateral pharyngeal walls (from 15.8 ± 6.3 cm^3 to 20.1 ± 8.9 cm^3; $p < 0.001$). In both groups, there was an inverse correlation between the increase in lateral pharyngeal wall volume and the reduction in the anteroposterior diameter of the retropalatal airway ($r = -0.54$; $p = 0.019$).

In the OSA group, there was posterior displacement of the tongue, as identified by a reduction in the tongue-pharyngeal distance from wakefulness to sleep (from 1.89 ± 0.28 cm to 1.62 ± 0.32 cm; $p = 0.001$), as shown in Table 2. In both groups, there was a direct correlation between the state-dependent change in the tongue-pharyngeal distance and that in

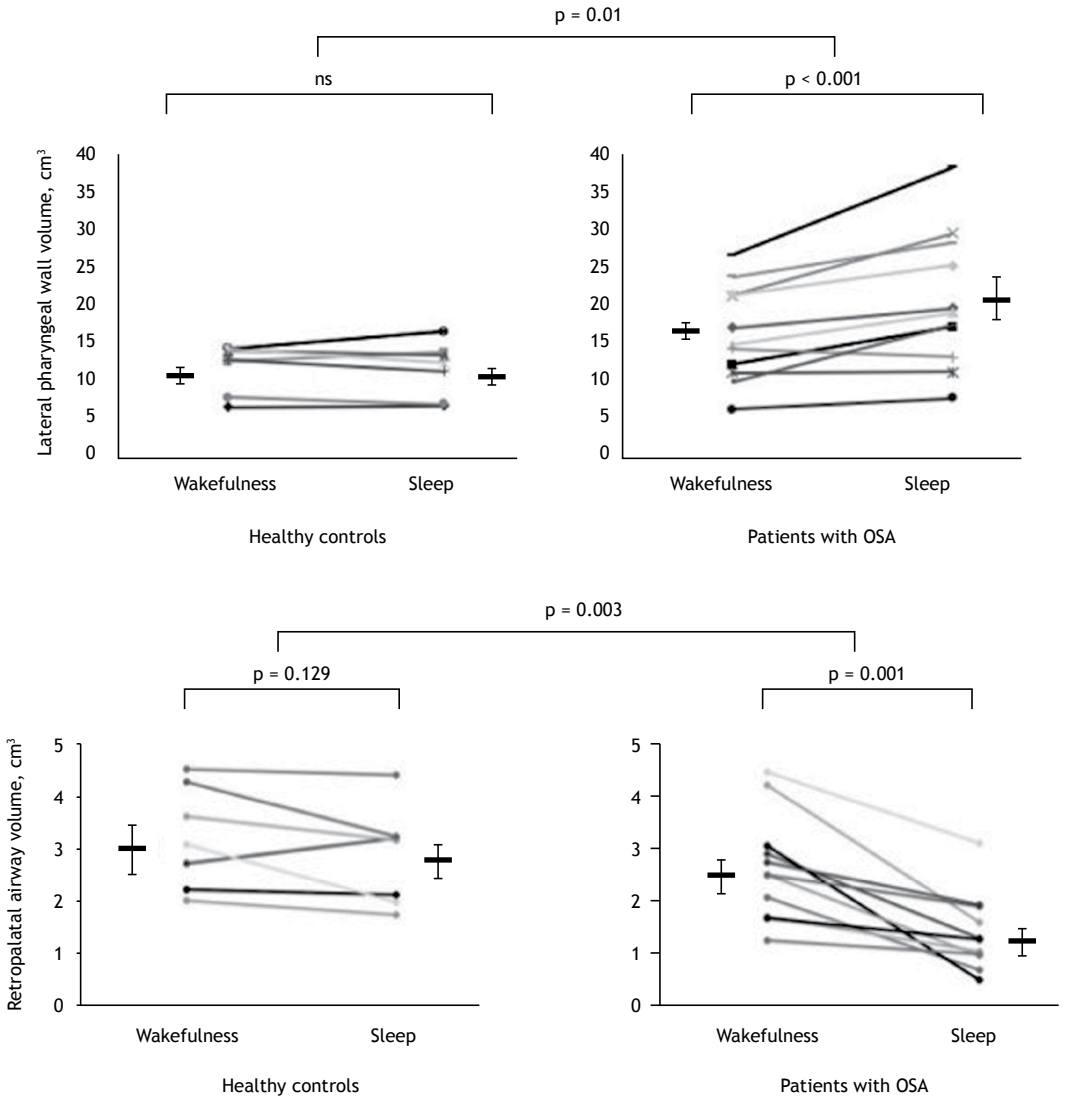

Figure 4. Individual changes in retropalatal upper airway volume and lateral pharyngeal wall volume (A and B, respectively) from the waking state to the sleep state among control and obstructive sleep apnea (OSA) group subjects. Short horizontal lines and bars indicate means and standard deviations, respectively. ns: not significant.

the anteroposterior diameter of the retropalatal airway ($r = 0.77$; $p < 0.001$), suggesting that the posterior displacement of the tongue during sleep is associated with anteroposterior narrowing of the retropalatal airway. Intraobserver agreement for lateral pharyngeal wall volume during wakefulness, determined from two measurements in each of 5 OSA group subjects, was high (intraclass correlation coefficient = 0.997; $p < 0.001$).

DISCUSSION

Here, we have demonstrated that upper airway narrowing (from the waking state to the sleep state) occurs predominantly at the retropalatal level in patients with OSA and in healthy individuals. Among the OSA group subjects, the most important findings were the following: upper airway narrowing occurred at the retropalatal level; upper airway narrowing occurred in the lateral and anteroposterior dimensions of the retropalatal airway; narrowing of the lateral and anteroposterior dimensions of the retropalatal airway was due to an increase in the lateral pharyngeal wall volume and posterior displacement of the tongue, respectively. These findings are consistent with the concept that the pharynx is a complex and interdependent cylinder that can narrow as the result of dynamic changes in the lateral walls and tongue position from wakefulness to sleep.

Sleep studies employing DISE have shown that the upper airway typically collapses at the retropalatal level.[28-31] Although endoscopy provides direct visualization of the pharyngeal lumen, it does not provide any insights into the behavior of the

surrounding structures. However, DISE has also shown retroglossal obstruction in some patients. One study demonstrated poor agreement between endoscopy and CT.[32] Possible explanations would be the use of sedation in endoscopy (i.e., DISE) and the inability to evaluate the retropalatal and retroglossal airways simultaneously. Retroglossal collapse can be secondary to retropalatal failure, due to negative pharyngeal pressure. Another study showed that compliance is lower in the retroglossal region than in the retropalatal region.[33] In this context, upper airway imaging studies, despite their demonstrable superiority, have not been widely used, because of major technical limitations. We were successful for several reasons. First, we used multidetector CT with 3D reconstructions. This technique allowed rapid (≤ 6 s) acquisition with high resolution, thus minimizing artifacts. Second, in contrast to MRI,[18-21] CT scanning allowed sleep monitoring with standard full polysomnography. In a CT sleep study involving 4 subjects, Stein et al.[22] showed that airway narrowing from the waking to the sleep state was greatest at the retropalatal level. Horner et al.[24] also used CT scans during wakefulness and sleep to evaluate 8 patients with OSA, demonstrating that the retropalatal region was the primary site of airway collapse.[19] In a study comparing MRI and pharyngeal endoscopy during sedation in 24 patients with OSA and 9 patients with non-sleep-apnea snoring, Suto et al.[19] found that both imaging methods showed changes occurring primarily at the retropalatal level. Barrera et al.[21] were able to obtain real-time MRI images in patients with OSA and controls. Although the authors also found that the retropalatal region was the most common site of obstruction, they did not assess the pattern of collapse or the behavior of the soft palate and lateral walls during upper airway obstruction. Trudo et al.[18] reported detailed upper airway dimensions during wakefulness and sleep; although they studied only subjects without OSA, they observed concomitant reductions in the anteroposterior and lateral dimensions of the retropalatal airway, which is in line with our observations. In contrast, Horner et al.[24] showed that, among the 8 patients with OSA evaluated in their study, anteroposterior narrowing occurred in 6, whereas lateral narrowing occurred in only 2. In the present study, we found that the retropalatal region was the primary site of upper airway obstruction during sleep in patients with OSA and that such obstruction resulted from concomitant anteroposterior and lateral narrowing.

In the present study, imaging was performed during natural, well-documented sleep and showed that the reduction in upper airway volume occurred mainly at the retropalatal level in patients with OSA and in healthy controls. In contrast, the retroglossal region did not change significantly from the waking to the sleep state. These findings are in line with those of a previous study.[18] In our OSA group subjects, anteroposterior narrowing of the retropalatal airway was associated with posterior displacement of the tongue and an increase in the lateral pharyngeal wall volume. The posterior third of the oral tongue lies in front of the soft palate, whereas the base of the tongue is in direct contact with the pharyngeal lumen. Due to its close proximity to the soft palate, the posterior third of the oral tongue can play an important role in retropalatal airway narrowing.[31]

Here, we have shown that the volume of the lateral pharyngeal walls increases during sleep in patients with OSA. A study evaluating only individuals without OSA showed an increase in the lateral pharyngeal wall thickness from wakefulness to sleep.[18] Previous studies have demonstrated that continuous positive airway pressure (CPAP),[34] mandibular advancement devices,[35] and tongue stabilizing devices[14] increase the lateral diameter of the retropalatal airway. The use of CPAP has also been shown to decrease lateral pharyngeal wall thickness.[34] Because the base of the tongue is connected to the lateral walls of the soft palate via the palatoglossal arch, it has been suggested that airway splinting (with CPAP) and tongue protrusion (with mandibular advancement devices or tongue stabilizing devices) stretch those connections, thus increasing the lateral dimensions of the retropalatal airway.[36] We speculate that the opposite occurs during sleep, when the posterior displacement of the tongue relaxes its connections with the retropalatal lateral walls, allowing folding of the lateral walls of the soft palate and a consequent increase in lateral pharyngeal wall volume. The position and configuration of the tongue, soft palate, and lateral pharyngeal walls are interdependent.

Our study has several potential limitations. First, we studied only men, and caution should therefore be used in extrapolating our results to women. Second, we employed CT, which exposes subjects to radiation and does not allow continuous image acquisition. In addition, we chose to obtain images of the upper airway during obstructive respiratory events in patients with severe OSA. Therefore, the pattern of upper airway obstruction might be different in patients with milder forms of the disorder. Furthermore, image acquisition in our study was not respiratory-gated and might therefore have been subject to respiratory cycle variability. However, the expected variability within a single respiratory cycle is small. Moreover, the number of healthy (control) subjects was small and the control group subjects were not matched to the OSA group subjects for age and BMI. Therefore, the differences between the two groups might have been influenced by the BMI and age. Despite the limited power of the present study to detect differences in airway dimensions, our findings in normal subjects during sleep are similar to those of a previous study.[18] Therefore, our control group provided confirmatory data. More importantly, our study was primarily designed to describe the dynamics of airway obstruction during obstructive respiratory events in patients with OSA.

In summary, our findings show that upper airway narrowing occurs predominantly at the retropalatal

level among male patients with severe OSA and among healthy male controls. Patients with OSA present with upper airway obstruction resulting from narrowing of the lateral and anteroposterior dimensions of the retropalatal airway during sleep. Such obstruction occurs due to an increase in the lateral pharyngeal wall volume and posterior displacement of the tongue. These findings highlight the complex dynamic interactions that occur among pharyngeal soft tissue structures during airway obstruction.

AUTHOR CONTRIBUTIONS

Passos UL—conception of the work, data collection, drafting the article; Genta PR—data analysis and interpretation, critical revision of the article; Marcondes BF—data collection, drafting the article; Lorenzi-Filho G—critical revision of the article, final approval of the version to be published; Gebrim EMMS—conception of the work, critical revision of the article, final approval of the version to be published.

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Prevalence of smoking and reasons for continuing to smoke: a population-based study

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ABSTRACT

Objective: To investigate the prevalence of smoking and the reasons for continuing to smoke among adults in Brazil. **Methods:** This was a cross-sectional, population-based study including 1,054 individuals ≥ 40 years of age, residents of the city of Florianopolis, Brazil, of whom 183 were smokers. All of the smokers completed the University of São Paulo Reasons for Smoking Scale (USP-RSS). Depressive symptoms were evaluated with the Hospital Anxiety and Depression Scale, and spirometry was performed to screen for COPD. **Results:** Of the 183 smokers, 105 (57.4%) were female, 138 (75.4%) were White, and 125 (63.8%) were in a low economic class. The mean level of education among the smokers was 9.6 ± 6.1 years. The mean smoking history was 29 ± 15 pack-years, 59% of the men having a ≥ 30 pack-year smoking history. Approximately 20% of the smokers had COPD, and 29% had depressive symptoms, which were more common in the women. The USP-RSS scores were highest for the pleasure of smoking (PS), tension reduction (TR), and physical dependence (PD) domains (3.9 ± 1.1, 3.6 ± 1.2, and 3.5 ± 1.3, respectively). Scores for the PS, TR, and weight control (WC) domains were significantly higher in women. Smokers with a > 20 pack-year smoking history scored significantly higher on the PD, PS, automatism, and close association (CA) domains. Smoking history was associated with the PD, PS, TR, and CA domains. Depressive symptoms were associated with the PD, social smoking, and CA domains ($p = 0.001$; $p = 0.01$; $p = 0.09$, respectively). Female gender and a low level of education were associated with the PS domain ($p = 0.04$) and TR domain ($p < 0.001$). **Conclusions:** The prevalence of smoking in our sample was relatively high (17.4%). The USP-RSS domains PS, TR, and WC explain why individuals continue smoking, as do depressive symptoms.

Keywords: Smoking/epidemiology; Tobacco use disorder/psychology; Smoking cessation/methods; Prevalence.

INTRODUCTION

According to the World Health Organization, smoking is associated with mental and behavioral disorders because of the accompanying dependence on nicotine, which is the main psychoactive substance in tobacco. Nicotine dependence is the primary factor in maintaining smoking behavior among adult smokers.[1] It is well documented that racial and ethnic differences can have a significant influence on the prevalence, patterns, health implications, and consequences of smoking, as well as on the efficacy of smoking cessation interventions.[2]

It is estimated that approximately one billion smokers consume six trillion cigarettes annually worldwide and that 10 million individuals will die from smoking-related diseases by 2030.[1] The prevalence of smoking varies across countries, China, India, Indonesia, Russia, the United States, Japan, Bangladesh, Germany, Turkey, and Brazil collectively accounting for over 16% of all smokers worldwide.[3]

The prevalence of smoking in Brazil varies by region, ranging from 5.1% in the city of Salvador, located in the northeastern region (in the state of Bahia), to 14.0% in the city of Curitiba, located in the southern region (in the state of Paraná), and by age group, being higher among adults in the 45- to 64-year age group.[4] In the cities of Fortaleza (located in the northeastern region, in the state of Ceará) and Macapá (located in the northern region, in the state of Amapá), the prevalence of smoking is 7.3% and 8.8% respectively. In the city of São Paulo (located in the southeastern region, in the state of São Paulo), the prevalence of smoking is 13.2%, compared with 13.6% and 10.1%, respectively, in the cities of Porto Alegre (in the state of Rio Grande do Sul) and Florianópolis (in the state of Santa Catarina), both of which are in the southern region.[4] It is noteworthy that, regardless of region, the prevalence of smoking in Brazil is higher among males than among females (12.7% vs. 8.0%).[4]

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Understanding the motivations that lead an individual to smoke is relevant because such an understanding can aid in preventing dependence and encouraging smoking cessation. Most previous studies have focused on the motivations to quit smoking, little emphasis having been placed on providing clear information about the motivations to continue smoking. Therefore, the aim of this population-based study was to identify the reasons to continue to smoking among smokers in the southern region of Brazil, through the use of standardized methodology and a validated scale.

METHODS

This was a cross-sectional, population-based study involving home interviews in the city of Florianopolis and including adults ≥ 40 years of age. We interviewed current smokers, using questionnaires that have been validated for use in Brazil,[5-8] in order to collect information about their motivations to smoke. The interviews were conducted between April of 2012 and February of 2013. Each interview took, on average, 90 min to complete. This study was conducted in accordance with the methodology employed in the Latin American Project for Research in Pulmonary Obstruction study[6] and the *Respira Floripa* (Breathe Floripa) study.[9]

The study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (Reference no. 1136). All participants gave written informed consent. The research was also conducted in accordance with the principles of the Declaration of Helsinki.[10]

The participants were invited to complete the following questionnaires: the Latin American Project for Research in Pulmonary Obstruction/Breathe Floripa questionnaire[6]; the Hospital Anxiety and Depression Scale (HADS)[7,8]; and the University of São Paulo Reasons for Smoking Scale (USP-RSS).[5]

The USP-RSS is a self-report questionnaire that assesses the motivations for smoking. It has been translated to Portuguese, culturally adapted for use in Brazil, and validated for such use.[5] Participants completed the USP-RSS individually. The 21 questions are divided into nine subscales: addiction (items 5-19); deriving pleasure from smoking (items 3-11); tension reduction (items 4, 12, and 18); stimulation (items 1, 9, and 16); automatism (items 7, 14, and 20); handling (items 2-10); social smoking (items 8-15); weight control (items 13-21); and affiliative attachment (items 6-17). Each response is scored on a Likert scale that ranges from 1 to 5, a score of 1 corresponding to a response of "never" and a score of 5 corresponding to a response of "always". Higher scores indicate greater motivation. The total score quantifies the overall level of motivation, and the subscale scores qualify that motivation. For the purposes of the present study, we established the following factors, hereafter referred to as domains, related the motivations to continue smoking: physical dependence (nicotine dependence); pleasure of smoking (pleasure-seeking); tension reduction (use of cigarettes to relax); stimulus (demand increasing concentration); automatism (smoking without thinking); handling (pleasure derived from manipulating and lighting a cigarette); social smoking (as a facilitator of social interaction); weight control (smoking to lose or maintain weight); and close association ("affiliative attachment" in the original version of the USP-RSS, defined as a strong emotional connection to all experienced situations),[5] the object (e.g., the cigarette) being transformed into a friend.

We evaluated the following variables: the USP-RSS scores, gender, race, economic class, level of education, smoking history, diagnosis of COPD (yes or no), and depressive symptoms (yes or no). We excluded smokers who met any of the following criteria: having been diagnosed with a psychiatric disorder that would limit their ability to understand and complete the questionnaire; having a history of long-term institutionalization; having recently undergone surgery; being pregnant; having had angina or acute myocardial infarction in the last three months; having active tuberculosis; and having arterial hypertension.

Sample size

The sample size calculation was based on the prevalence of COPD in the city of São Paulo, which ranges from 7.8% to 19.7% according to data from the study conducted by Menezes et al.[6] The calculation also considered a margin of error of four percentage points and a 20% margin of safety for non-response and losses. We thus estimated that a sample of approximately 1,000 subjects would be required. To obtain a representative sample that would allow further group analysis, we selected 846 residences housing a collective total of 1,192 individuals. All of the participants who described themselves as smokers were asked to complete the USP-RSS.[5]

Sampling procedure

Given the estimated 1.4 individuals ≥ 40 years of age per household, we randomly selected 68 of the 419 census tracts in the city of Florianopolis, comprising a total of 846 residences. To obtain a representative sample of adults living in Florianopolis, we applied a cluster sampling strategy, in which economic status (purchasing power, classified as determined by the Brazilian Market Research Association and based on the Brazilian national minimum wage)[11] was specified as follows: class A—heads of households in which the total monthly income is more than 20 times the minimum wage; class B—heads of households in which the total monthly income is 10-20 times the minimum wage; class C—heads of households in which the total monthly income is 3-10 times the minimum wage; class D—heads of households in which the total monthly income is 1-3 times the minimum wage; and class E—heads of households in which the total monthly income is equal to or less than the minimum wage.

Study definitions

Participants were categorized as smokers if they had smoked at least 100 cigarettes during their lifetime and reported that they were currently smoking at the time of the interview.[12] A diagnosis of COPD was defined by the presence of airflow limitation, as identified by an FEV_1/FVC ratio < 0.70 after bronchodilator administration.[13]

Because the study design was based primarily on the prevalence of COPD, we included data on symptoms of depression only if the HADS score was ≥ 8 points.[14] The HADS anxiety data were not considered, because evaluating anxiety was not one of the study objectives.

Methodology

Spirometry

Before and after administration of a bronchodilator (albuterol, 200 µg), spirometry maneuvers were performed in accordance with the American Thoracic Society criteria.[15] We employed a portable spirometer (EasyOne; ndd Medical Technologies, Zurich, Switzerland), the calibration of which was checked following the manufacturer's guidelines. All spirometry procedures were analyzed by two pulmonologists with expertise in pulmonary function testing, and the predicted values were calculated from the equations proposed in the National Health and Nutrition Examination Survey.[16]

Statistical analysis

The completed questionnaires were coded by the interviewers and reviewed by the supervisors. Data were selected and double entered into a database. The results are presented as means and standard deviations or as absolute and relative frequencies. The variables were analyzed with Student's t-tests. To compare the means among three or more groups, we used ANOVA. Logistic regression was used in order to analyze descriptive data or to determine whether the various domains or motivational factors for smoking (dependent variable) correlated with the descriptors of interest (independent variables). Odds ratios and their 95% confidence intervals were calculated for each independent variable. For all analyses, values of $p < 0.05$ were considered significant. Data were analyzed with the Predictive Analytics Software package, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

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RESULTS

Five of the 846 selected households were not visited because of an inability to contact the residents. Of the 1,192 eligible residents, 110 declined to participate in the study. The remaining individuals (n = 1,082) completed all of the steps, corresponding to a response rate of 90.8%. Subsequently, 23 interviews were excluded from the analysis because of participant inability to perform the maneuvers required to obtain reproducible flow-volume curves during spirometry. Therefore, we evaluated 1,059 individuals (88.8% of the eligible population), 188 of whom were categorized as current smokers. Finally, 5 smokers were excluded because they did not answer all of the questions on the USP-RSS. Consequently, the final sample comprised 1,054 individuals, and the prevalence of smoking in the sample was 17.4%.

The sociodemographic and clinical characteristics of the 183 smokers who completed the USP-RSS are detailed in Table 1. There was a slight, although less than significant, predominance of women, who accounted for 57.4% of the smokers, which was to be expected because there are more women than men in the city of Florianopolis, as shown in the Brazilian Institute of Geography and Statistics data for 2010.[17] Despite the predominance of female smokers, the number of cigarettes smoked by women, expressed in pack-years, was significantly lower than the number smoked by men, a smoking history greater than 30 pack-years being observed in 59% of the men, compared with 39% of the women ($p = 0.01$). Most (75.4%) of the smokers reported their race as White. In relation to the economic class, 63.8% of the smokers were in class C, 18.6% were in class D or E, 8.2% were in class A, and 4.9% were in class B (Table 1). A functional diagnosis of COPD was made in 19.7% of the smokers evaluated. Symptoms of depression, screened with the HADS depression subscale, were identified in 29.5% of the smokers, with a significant predominance in women ($p = 0.002$).

Table 2 shows the mean scores for the USP-RSS domains studied. The domains for which the scores were highest were as follows: pleasure of smoking (mean, 3.9 ± 1.1); tension reduction (mean, 3.6 ± 1.2); and physical dependence (mean, 3.5 ± 1.3). In addition, significant differences were observed between the men and the women in relation to the mean scores for the following domains: pleasure of smoking (3.7 ± 1.3 vs. 4.1 ± 1.2, $p = 0.01$); tension reduction (3.4 ± 1.2 vs. 4.0 ± 1.2, $p = 0.005$); and weight control (1.7 ± 1.2 vs. 2.4 ± 1.6, $p = 0.002$).

Individuals with 0-4 years of schooling had significantly higher scores than did the other participants for the following motivational domains: pleasure of smoking ($p = 0.04$); tension reduction ($p = 0.03$); stimulus ($p = 0.001$); handling ($p = 0.009$); social smoking ($p = 0.02$); and close association ($p = 0.001$). Individuals who reported a smoking history > 21 pack-years had significantly higher scores for the domains of physical dependence ($p < 0.001$), pleasure of smoking ($p = 0.004$), automatism ($p < 0.001$), and close association ($p = 0.006$).

Individuals who presented symptoms or a functional diagnosis of COPD had significantly higher USP-RSS scores than did those without COPD only in the physical dependence domain ($p = 0.03$) and close association domain ($p = 0.03$). Individuals with depressive

Table 1. Sociodemographic and clinical characteristics of the smokers evaluated.

Characteristic	(n = 183)
Age, in years, mean ± SD	54.5 ± 9.2
Gender, n (%)	
Female	105 (57.4)
Male	78 (42.6)
Self-reported race, n (%)	
White	138 (75.4)
Other	45 (24.6)
Economic class, n (%)	
A	15 (8.2)
B	9 (4.9)
C	125 (63.8)
D/E	34 (18.6)
Years of schooling, mean ± SD	9.6 ± 6.1
Smoking history, in pack-years, mean ± SD	29 ± 15
COPD, n (%)	36 (19.7)
Symptoms of depression, n (%)	54 (29.5)

Table 2. University of São Paulo Reasons for Smoking Scale scores, for the sample as a whole and by gender.[a]

USP-RSS domain	Total (n = 183)	Male (n = 78)	Female (n = 105)	p*
Physical dependence	3.5 ± 1.3	3.4 ± 1.3	3.5 ± 1.3	0.3
Pleasure of smoking	3.9 ± 1.1	3.7 ± 1.3	4.1 ± 1.2	0.01
Tension reduction	3.6 ± 1.2	3.4 ± 1.2	4.0 ± 1.2	0.005
Stimulus	2.5 ± 1.2	2.3 ± 1.2	2.6 ± 1.4	0.3
Automatism	2.2 ± 1.2	2.1 ± 1.1	2.2 ± 1.1	0.9
Handling	2.8 ± 1.3	3.4 ± 1.3	3.5 ± 1.3	0.5
Social smoking	2.2 ± 1.3	2.1 ± 1.2	2.2 ± 1.4	0.5
Weight control	2.1 ± 1.5	1.7 ± 1.2	2.4 ± 1.6	0.002
Close association	2.9 ± 1.4	2.9 ± 1.3	3.0 ± 1.4	0.7

USP-RSS: University of São Paulo Reasons for Smoking Scale. [a]Data are presented as mean ± standard deviation. *Unpaired t-test.

symptoms scored significantly higher than did those without on the following domains: physical dependence ($p = 0.007$); tension reduction ($p = 0.001$); stimulus ($p < 0.001$); social smoking ($p < 0.001$); weight control ($p = 0.01$); and close association ($p < 0.001$).

Table 3 shows the results of the logistic regression analysis, performed to evaluate the effects that gender, smoking history, level of education, presence of depressive symptoms, and COPD have on the following domains: physical dependence, pleasure of smoking, tension reduction, stimulus, automatism, handling, social smoking, weight control, and close association. The main determinants of the score for the physical dependence domain were a smoking history of 21-30 pack-years (OR = 15.8; 95% CI: 3.9-63.2; $p < 0.001$) and the presence of depression symptoms (OR = 3.7; 95% CI: 1.7-8.1; $p = 0.001$). A smoking history > 30 pack-years was also the main determinant of the scores for the following domains: pleasure of smoking (OR = 5.7; 95% CI: 2.2-52.7; $p > 0.001$); tension reduction (OR = 4.6; 95% CI: 1.7-7.4; $p = 0.006$); and close association (OR = 3.5; 95% CI: 1.1-11.2; $p = 0.02$). Depressive symptoms were significantly associated with the physical dependence, social smoking, and close association domains ($p = 0.001$, $p = 0.01$, and $p = 0.009$, respectively). Female gender and a low level of education were key determinants of the scores for the pleasure of smoking and tension reduction domains ($p = 0.04$ and $p < 0.001$, respectively). None of the variables studied were found to be determinants of the scores for the domains of automatism and handling ($p > 0.05$).

DISCUSSION

In this population-based study, we employed a robust methodology to evaluate the prevalence and characteristics of smoking, as well as aspects related to the motivations to continue smoking, among individuals 40 years of age or older. Our findings show that the prevalence of smoking was relatively high (17.4%) in our sample. In addition, our data suggest that low economic class and a low level of education are characteristic of smokers. We also found that, although there were more female smokers than male smokers in our sample, the men had greater smoking histories.

Among the main findings were the fact that the USP-RSS scores were highest for the pleasure of smoking, tension reduction, and physical dependence

Table 3. Logistic regression analysis of the determinants of the scores for the University of São Paulo Reasons for Smoking Scale domains.

USP-RSS domain Determinant	OR	95% CI	p*
Physical dependence			
Smoking history			
< 10 pack-years	–	–	–
11-20 pack-years	6.2	(1.6-26.8)	0.009
21-30 pack-years	15.8	(3.9-63.2)	< 0.001
> 30 pack-years	15.1	(4.3-52.7)	< 0.001
Symptoms of depression	3.7	(1.7-8.1)	0.001
Pleasure of smoking			
Smoking history			
< 10 pack-years	–		–
11-20 pack-years	–		–
21-30 pack-years	3.9	(1.3-12.0)	0.01
> 30 pack-years	5.7	(2.2-52.7)	< 0.001
Female gender	2.1	(1.0-4.3)	0.04
≤ 4 years of schooling	2.7	(1.0-7.0)	0.04
Tension reduction			
Smoking history			
< 10 pack-years	–		–
11-20 pack-years	4.3	(1.3-14.4)	0.01
21-30 pack-years	–		–
> 30 pack-years	4.6	(1.7-7.4)	0.006
Female gender	3.5	(1.0-4.3)	< 0.001
Level of education			
≤ 4 years of schooling	6.6	(2.3-18.8)	< 0.001
5-8 years of schooling	4.9	(1.7-14.4)	0.004
9-12 years of schooling	4.3	(1.5-12.0)	0.004
≥ 13 years of schooling	–		–
Stimulus			
≤ 4 years of schooling	5.9	(1.2-29.1)	0.03
Symptoms of depression	3.6	(1.4-8.8)	0.006
Automatism	–	–	–
Handling	–	–	–
Social smoking			
Symptoms of depression	3.2	(1.3-7.7)	0.01
Weight control			
Female gender	3.4	(1.3-9.1)	0.01
Close association			
COPD	3.2	(1.4-7.8)	0.007
Symptoms of depression	2.7	(1.2-5.5)	0.009
> 30 pack-year smoking history	3.5	(1.1-11.2)	0.02

USP-RSS: University of São Paulo Reasons for Smoking Scale.

domains, the scores for the pleasure of smoking, tension reduction, and weight control domains being significantly higher in women. Smokers with a smoking history greater than 20 pack-years scored significantly higher on the physical dependence, pleasure of smoking, automatism, and close association domains. In addition, female gender and a low level of education were key determinants of the scores on the pleasure of smoking and tension reduction domains. For women, the pleasure of smoking, tension reduction, and weight control domains, as well as symptoms of depression, are essential aspects to consider in personalized smoking cessation treatment. The association identified between a greater smoking history and the motivational profile, including the pleasure of smoking, tension reduction, and physical dependence domains, could contribute to the future development of novel smoking cessation strategies.

To our knowledge, this is the first population-based study investigating the reasons to continue smoking among smokers in Brazil. We chose to apply the USP-RSS because it is the result of careful work. As

previously stated, the USP-RSS has been translated to Portuguese, culturally adapted for use in Brazil, and validated for such use.[5] However, it can be used in other countries, given that it is well constructed and is easily implemented in clinical practice.

The physical dependence, stimulus, handling, social smoking, and close association domains are common to both genders. That could be attributed to the release of mediators in the dopamine reward system. In addition, physical addiction to nicotine may be determined by genes (e.g., the *SLC6A3* gene) and dopamine transport, both of which are regulated by the central nervous system. The dopamine D2 and D4 receptor polymorphisms have been shown to be more common in smokers than in nonsmokers.[18,19] In addition, smokers exhibit a significant deficit in dopamine regulation, which requires external stimulus, such as exogenous nicotine, in order to release quantities sufficient to produce pleasurable feelings.[18,19] Other studies have also reported a correlation between nicotine dependence and continued smoking, emphasizing the fact that such dependence is not the only motivational factor for smoking and that more comprehensive studies should be conducted to improve the understanding of the complex relationship between smoking and motivational factors.[20,21]

Other relevant findings of the present study were related to the functional diagnosis of COPD and the presence of depressive symptoms. Although the individuals evaluated were aware of the fact that COPD is a serious illness that results in significant pulmonary dysfunction, 19.7% of the smokers with COPD continued to smoke because they had established an intense emotional link (i.e., a close association) with smoking. In addition, there is evidence that depressed smokers are more motivated to smoke, in order to relieve negative feelings such as anxiety, anger, fear, sadness, and shame.[22,23] Our analysis of the USP-RSS domain scores confirmed those findings.

In the present study, the presence of depressive symptoms, a diagnosis of COPD, and a smoking history greater than 30 pack-years were found to correlate with a close association with smoking. However, our findings should be interpreted with caution, because those factors are influenced by the close relationships among depression, COPD, and smoking. One possible explanation for these findings is that the associations among depressive symptoms, COPD, and smoking history are only a reflection of the physical dependence or depressive symptoms. However, our findings are inconclusive and require further investigation.

We found that social smoking, also known as intermittent smoking, was predominantly associated with depressive symptoms. Although that finding may be due to the age of the individuals in the study sample (≥ 40 years), these are important data that should not be ignored. A recent study describing the motivational profile of adolescents also showed higher scores in the social smoking domain.[24]

In the present study, we applied a reliable, validated instrument that provides motivational intensity scores related to smoking in adults. In our sample of 183 smokers ≥ 40 years of age, we found that the main reasons for continuing to smoke were related to the pleasure of smoking, tension reduction, and physical dependence domains. In addition, we demonstrated some differences between women and men in relation to the determinants of continued smoking. The determinants of the motivational domains pleasure of smoking, stress reduction, and weight control were found to be more common in females. The individual reasons for continuing to smoke identified in this study may contribute to the development of novel targeted smoking cessation strategies.

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NACHT, LRR, and PYD domains-containing Protein 3 and LL-37: prognostic value of new biomarkers in community-acquired pneumonia

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ABSTRACT

Objective: This study aimed to determine the serum levels of NACHT, Leucine-rich repeat (LRR), and Pyrin (PYD) domains-containing Protein 3 (NLRP3) and cathelicidin LL-37, and investigate their prognostic significance in community-acquired pneumonia (CAP). **Methods:** The sample of this prospective study was composed of 76 consecutive patients with CAP. Demographic data and clinical characteristics were collected. Serum levels of NLRP3 and LL-37 were determined by ELISA. Spearman's analysis was used to evaluate the correlation between NLRP3 and LL-37. Association of NLRP3 and LL-37 with 30-day survival and mortality rates was assessed using the Kaplan-Meier curve and logistic regression analysis. **Results:** Serum NLRP3 significantly increased whereas serum LL-37 significantly decreased in patients with severe CAP. Significant correlation was observed between serum NLRP3 and LL-37 in CAP patients. Patients with higher levels of NLRP3 and lower levels of LL-37 showed lower 30-day survival rate and higher mortality compared with those with lower NLRP3 and higher LL-37 levels. **Conclusion:** Severe CAP patients tend to present higher serum NLRP3 and lower serum LL-37, which might serve as potential biomarkers for CAP prognosis.

Keywords: Community-acquired pneumonia; Prognosis; Biomarkers; Prospective study.

INTRODUCTION

Pneumonia is widely recognized as a significant public health problem, and one of the most common leading causes of hospitalization and death worldwide. It is classified into community-acquired (CAP) and hospital-acquired pneumonia according to environment where infection occurs.[1,2] Pulmonary parenchymal disease occurring outside of the hospital setting has traditionally been categorized as CAP, which still presents significant morbidity and mortality. The incidence of CAP ranges from 0.33% to 4.6% a year in the elderly population, depending on co-morbid and severity conditions.[3-5] Advances in medical care have improved survival in patients with severe CAP; however, for the majority of CAP patients, improvement in disease management is inconspicuous.[6] Therefore, it is a hotspot in which more reliable biomarkers should be sought.

To date, several serum biomarkers have been found to predict disease severity and prognosis in patients with CAP. For example, Kolditz et al.[7] conducted a prospective study and demonstrated that serum cortisol predicted mortality and critical disease in CAP patients regardless of clinical scores and inflammatory biomarkers. Angus et al.[8] found that serum high-mobility group box-1 levels were significantly higher in CAP patients than in healthy controls, and were associated with mortality. Moreover, Zhang et al.[9] identified N-Terminal pro-B-type brain natriuretic peptide (NT-pro BNP) as an effective predictor of adverse cardiac events in patients with CAP, which was positively correlated with the disease severity.

Host defense peptide LL-37, a fragment of the cathelicidin protein precursor hCAP18, has been previously identified as a potent regulator of inflammatory response.[10] In addition to its anti-infective properties, LL-37 also regulated the secretion and release of multiple inflammatory cytokines from immune cells. Jiao et al.[11] showed that LL-37 deteriorated asthma via activation of eosinophils interacting with bronchial epithelial cells. Furthermore, LL-37 has been reported to improve the survival of septic mice through inhibition of macrophage pyroptosis, inflammatory cytokine production, and bacterial growth.[12] However, the expression and clinical significance of LL-37 in the pathogenesis of CAP remains unclear.

Nod-like receptor protein 3 (NLRP3) plays an important role in the inflammation process in many diseases and bioprocesses.[13] Studies have shown NLRP3 is high in injury-induced inflammation, and activation of NLRP3 can promote pneumonia development.[14] However, few studies have focused on the clinical significance of serum NLRP3 in CAP patients. This study aimed to investigate the expression of LL-37 and NLRP3 in CAP patients. The present study may provide deeper insights in CAP and some new research targets for CAP treatment.

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METHODS

Study sample

This prospective study was conducted with 76 CAP patients and 50 healthy controls from the aforementioned Hospital between January 2015 and December 2016. Community-acquired pneumonia (CAP) was diagnosed based on lower respiratory tract symptoms, and confirmed by chest radiograph within 24h of hospital admission. Patients with health-care associated pneumonia and with autoimmune diseases were excluded from the survey. The pneumonia severity index (PSI) was used to categorize all patients into mild/moderate (PSI Risk Classes I-III) or severe (PSI Risk Classes IV-V) CAP, as previously described.(15) All experimental protocols were approved by the Research Ethics Committee of Jining No.1 People's Hospital. Informed consent was obtained from all subjects.

Data collection

Baseline assessment included age, gender, antimicrobial treatment prior to enrollment, clinical symptoms, laboratory data, PSI score, and mortality during a 30-day follow-up.

Laboratory test

Venous blood samples were collected within 24h of hospital admission and stored at -70 °C. White blood cell (WBC) count was determined by the hospital laboratory. ELISA was performed using commercial kits for the quantitative measurements of C-reactive protein (CRP; Roche Diagnostics, Almere, The Netherlands), NLRP3 (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China), and LL-37 (Hycult Biotechnology, Uden, The Netherlands), according to the manufacturer's protocol.

Statistical analysis

Continuous variables were presented as mean ± standard deviation if normally distributed, or as median if otherwise, and were compared using the Wilcoxon-Mann-Whitney test, whereas comparisons between groups on categorical variables were carried out using the Chi square test. Spearman's rank correlation coefficient analysis was performed to determine the relationship between serum NLRP3 and LL-37 levels. The Kaplan-Meier method was applied to estimate survival analysis. The correlation between CRP, NLRP3 and LL-37 serum levels and 30-day mortality in all patients was carried out using logistic multivariate regression analysis. A significance value of $p<0.05$ was adopted for all statistical analyses, which were processed using the SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software.

RESULTS

Patient characteristics

In total, 76 patients with CAP were included in this study, and their demographic data and clinical characteristics are shown in Table 1. There were no significant differences between mild/moderate or severe CAP patients regarding age, gender, antimicrobial treatment prior to enrollment, and clinical symptoms. Patients with severe CAP exhibited significantly increased serum CRP and NLRP3 levels and WBC counts, as well as lower serum LL-37 levels and higher rates for PSI Risk Classes IV-V and mortality during a 30-day follow-up compared with those with mild/moderate CAP (all with $p<0.05$).

Correlation analysis of serum NLRP3 and LL-37 levels

Serum levels of NLRP3 and LL-37 were further compared in CAP patients with those in the healthy controls, and the ELISA assay indicated higher serum NLRP3 and LL-37 levels in patients with CAP than in healthy controls (Figure 1A; $p<0.05$). Spearman's correlation analysis demonstrated that serum NLRP3 was negatively correlated with serum LL-37 (Figure 1B; $p<0.05$).

Relationship between NLRP3 and LL-37 and clinical parameters

To further determine clinical significance of NLRP3 and LL-37, all patients were categorized into NLRP3 or LL-37 high/low groups according to mean ± standard deviation or median values. Table 2 shows that patients with higher serum NLRP3 or lower serum LL-37 levels had higher serum CRP levels, WBC counts, and mortality rate during a 30-day follow-up than those with lower serum NLRP3 or higher serum LL-37 levels (all with $p<0.05$). In addition, more patients in PSI Risk Classes I-III (PSI ≤90 points) and IV-V (PSI >90 points) were included in patients with higher serum NLRP3 or lower serum LL-37 levels compared with those with lower serum NLRP3 or higher serum LL-37 levels (all with $p<0.05$).

Association between NLRP3 and LL-37 and 30-day survival and mortality rates

Prognostic relevance of serum NLRP3 and LL-37 levels in CAP patients was also assessed. Kaplan-Meier survival curves revealed that patients with high serum NLRP3 or LL-37 levels showed lower survival rates than those with low serum NLRP3 or LL-37 levels (all with $p<0.05$) according to the log-rank test (Figure 1C).

Multivariate logistic regression was then conducted based on the aforementioned results. As shown in Table 3, both higher serum NLRP3 and lower serum LL-37 conducted were closely associated with the 30-day mortality rate in CAP patients (Table 4).

DISCUSSION

Community-acquired pneumonia (CAP) is a common infectious disease associated with significant morbidity and mortality that poses a major threat to human health worldwide.[16] Despite the major mortality

Table 1. Basic clinical information on the study participants.

Variables	Mild/moderate CAP, n = 41	Severe CAP, n = 35
Mean age (years)	59.3 ± 10.1	61.7 ± 12.6
Gender (male:female)	24:17	20:15
Antibiotics received before treatment; n (%)	21 (52.5)	16 (45.7)
Symptoms; n (%)		
Fever	19 (46.3)	18 (51.4)
Cough	15 (36.6)	15 (42.8)
Sputum	13 (31.7)	12 (34.2)
Shortness of breath	9 (21.9)	9 (25.7)
Chest pain	6 (14.6)	7 (20.0)
Laboratory		
CRP (mg/L)	63 (25~180)	130.5 (81~235)*
WBC (10^9/mL)	9.3 (7.1~14.4)	13.1 (10.2~17.5)*
NLRP3 (ng/mL)	31 (20~45)	49 (38~60*
LL-37 (ng/mL)	132 (87~195)	86 (39~124)*
PSI; n (%)		
PSI Risk Classes I-III	41 (100)	0 (0)
PSI Risk Classes IV-V	0 (0)	35 (100)*
Mortality during a 30-day follow-up; n (%)	7 (17.0)	12 (34.2)*

*$p<0.05$.

Table 2. Clinical outcomes in CAP patients with high/low serum LL-37 or NLRP3 levels.

Variables	Low LL-37; n = 39	High LL-37; n = 37	Low NLRP3; n = 38	High NLRP3; n = 38
Mean age (years)	59.6 ± 10.5	61.5 ± 11.8	60.3 ± 11.2	61.1 ± 12.3
Gender (male:female)	23: 16	21: 16	23:15	21:17
Antibiotics received before treatment; n (%)	19 (48.7)	18 (48.6)	18 (47.4)	19 (50.0)
Symptoms; n (%)				
Fever	20 (51.3)	17 (45.9)	17 (44.8)	20 (52.6)
Cough	14 (35.9)	16 (43.2)	14 (436.8)	16 (42.1)
Sputum	13 (33.3)	12 (32.4)	12 (31.2)	13 (34.2)
Shortness of breath	8 (20.5)	10 (27.0)	8 (21.1)	10 (26.3)
Chest pain	7 (17.9)	6 (16.2)	5 (13.2)	8 (21.1)
Laboratory				
CRP (mg/L)	137 (83~235)	68 (25~174)*	60 (25~169)	135 (84~235)#
WBC (10^9/mL)	12.9 (11.2~17.5)	9.3 (7.1~14.5)*	8.7 (7.1~13.8)	13.5 (11.0~17.5)#
NLRP3 (ng/mL)	50 (40~60)	30 (20~43)*	142 (90~195)	73 (39~120)#
PSI; n (%)				
PSI Risk Classes I-III	11(28.2)	30(81.1)*	32 (84.2)	9 (23.6)#
PSI Risk Classes IV-V	28 (71.8)	7(18.9)*	6 (15.8)	29 (76.3)#
Mortality during a 30-day follow-up; n (%)	13 (33.3)	6 (16.2)*	5 (13.2)	14 (36.8)#

*$p<0.05$, compared with the low LL-37 group; #$p<0.05$, compared with the low NLRP3 group.

Table 3. Correlation between serum NLRP3 and LL-37 levels with 30-day mortality for CAP patients by logistic multivariate regression analysis.

	Wald	Odds ratio	95% CI	p value
CRP	1.037	1.014	(0.852~1.243)	0.174
NLRP3	13.970	1.146	(1.067~1.231)	<0.001
LL-37	14.600	0.947	(0.921~0.974)	<0.001
PSI	0.765	1.574	(0.687~2.039)	0.421

CI: confidence index.

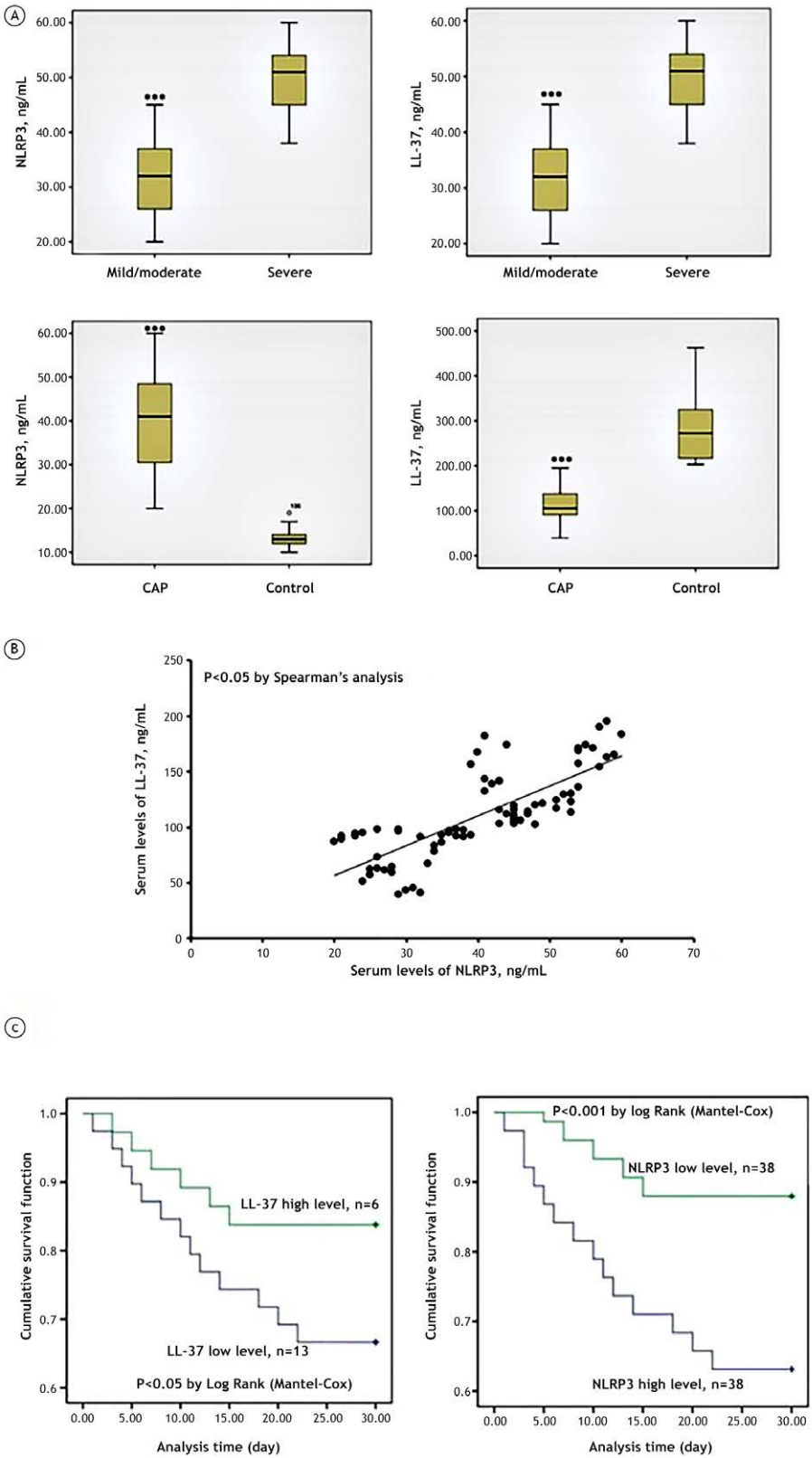

Figure 1. (A) Serum NLRP3 and LL-37 levels in patients with CAP (n=76) and healthy controls (n=50) and levels in patients with mild/moderate (n=41) or severe (n=35) CAP patients determined by ELISA. *p<0.05 vs. control group; (B) Correlation analysis between NLRP3 and LL-37 in CAP patients using Spearman's correlation analysis; (C) Kaplan-Meier survival curve of CAP patients with low or high serum NLRP3 or LL-37 levels.

Table 4. Clinic outcomes in CAP patients with high/low serum NLRP3.

Variable	Low NLRP3, n = 38	High NLRP3, n = 38
Mean age, years	60.3 ± 11.2	61.1 ± 12.3
Gender, male: female	23: 15	21: 17
Antibiotics received before treatment, n (%)	18 (47.4)	19 (50.0)
Symptoms, n (%)		
Fever	17 (44.8)	20 (52.6)
Cough	14 (436.8)	16 (42.1)
Sputum	12 (31.2)	13 (34.2)
Shortness of breath	8 (21.1)	10 (26.3)
Chest pain	5 (13.2)	8 (21.1)
Laboratory		
CRP, mg/L	60 (25~169)	135 (84~235)*
WBC, 10^9/mL	8.7 (7.1~13.8)	13.5 (11.0~17.5)*
LL-37, ng/mL	142 (90~195)	73 (39~120)*
PSI, n (%)		
I-III	32 (84.2)	9 (23.6)*
IV-V	6 (15.8)	29 (76.3)*
Mortality during 30 days follow-up, n (%)	5 (13.2)	14 (36.8)*

*$p<0.05$, compared with the low cortisol group.

rate observed,[4,17] at present, initial diagnosis of CAP mainly includes respiratory symptoms and general signs, which cannot accurately reflect the disease condition. Although invisible pulmonary lesions can be accurately localized by fluoroscopy, the current widely used chest CT and radiography are radioactive and relatively expensive.[18] Thus, there is an urgent need to discover and validate new serum biomarkers for CAP.

C-reactive protein (CRP) is an acute-phase protein produced by hepatic cells that is widely involved in various inflammatory processes.[19] Serum CRP levels are generally low in healthy people, whereas stress stimulations such as infection and organ and tissue damage can trigger significant increase in serum CRP, which is typically not susceptible to antibiotics, malnutrition, glucocorticoids, or immunosuppressant drugs.[20] CRP is the most commonly used biomarker in the diagnosis and treatment of CAP due to its inexpensive price and high sensitivity to inflammation.[21,22] In the present study, serum CRP levels were highly expressed in severe CAP patients compared with mild/moderate CAP patients.

The role of Nod-like receptor protein 3 (NLRP3) in inflammatory processes, including pneumonia, has been demonstrated in many studies. Van Lieshout et al.[23] showed the NLRP3 inflammasome impaired host defense during lethal pneumonia in mice. It was also found that *staphylococcus aureus* α-hemolysin could mediate virulence by activating the NLRP3 inflammasome in a murine model of severe pneumonia.[24] Nevertheless, few studies have demonstrated the clinical significance of NLRP3 in CAP patients. Finding of the present study revealed, for the first time, that serum NLRP3 was significantly up-regulated in CAP patients compared with healthy controls, as well as in patients with severe CAP compared with mild/moderate CAP patients. Further investigation elucidated that patients with higher serum NLRP3 levels had higher serum CRP and lower LL-37 levels, and higher WBC counts and 30-day mortality rate.

Antimicrobial peptide LL-37 is the only member of cathelicidin family in human innate immune system that is cleaved from a cationic antimicrobial polypeptide of 18-kDa. In addition to its broad antimicrobial activity, LL-37 plays a vital role in immune modulation, angiogenesis, wound healing, and anti-tumor.[25,26] It has been shown that LL-37 was significantly down-regulated in children with pneumonia.[27] Hou et al.[28] also found that LL-37 could inhibit LTA-induced inflammation and suppress the development of pneumonia in a mice model. However, whether serum LL-37 levels were associated with prognosis of CAP patients is unclear. Findings of the present study showed that serum LL-37 levels in CAP patients, especially in patients with severe CAP, were also significantly down-regulated, and that patients with lower serum LL-37 showed lower survival rates. Nevertheless, the present study also has some limitations: first, the study sample is limited; second, the underlying mechanisms for how NLRP3 and LL-37 affected CAP are unknown. These issues need to be confirmed in further studies.

In conclusion, a prospective study was conducted to investigate the clinical significance of NLRP3 and LL-37 in CAP patients. Results showed that NLRP3 was significantly high, whereas LL-37 was significant down-regulated in CAP patients, and that both NLRP3 and LL-37 were significantly correlated with prognosis for CAP patients. This study may provide more clinical evidence and deeper understanding regarding role of NLRP3 and LL-37 in CAP.

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Disability and its clinical correlates in pulmonary hypertension measured through the World Health Organization Disability Assessment Schedule 2.0: a prospective, observational study

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ABSTRACT

Objective: To characterise the degree of disability in pulmonary hypertension (PH) patients based on the World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0). **Method:** A prospective and observational study of patients with documented PH (N = 46). Patients completed the WHODAS 2.0 questionnaire during a scheduled routine clinical visit, and their demographic and clinical characteristics were retrieved from electronic medical records (EMR). In subsequent visits, selected clinical variables were registered to assess disease progression. **Results:** WHODAS 2.0 scores were indicative of mild to moderate disability for the domains of mobility (22.0 ± 23.2), life activities (23.7 ± 25.5), and participation in society (17.2 ± 15.9), as well as total WHODAS 2.0 score (15.3 ± 15.2). For the domains of cognition (9.1 ± 14.1), self-care (8.3 ± 14.4), and interpersonal relationships (11.7 ± 15.7), scores were lower. Disability scores were, generally, proportional to the PH severity. The main baseline correlates of disability were World Health Organisation (WHO) functional class, fatigue, dyspnoea, 6-minute walking distance (6MWD), and N-terminal pro b-type natriuretic peptide (NT-proBNP). Baseline WHODAS 2.0 scores showed significant associations with disease progression. However, this effect was not transversal to all domains, with only a few domains significantly associated with disease progression variables. **Conclusions:** This PH population shows mild disability, with higher degree of disability in the domains of mobility and life activities. This study is the first one to assess disability in PH using WHODAS 2.0. Further studies should apply this scale to larger PH populations with suitable representations of more severe PH forms.

Keywords: Pulmonary hypertension; International Classification of Functioning, Disability and Health; Disability evaluation; Quality of Life.

INTRODUCTION

Pulmonary hypertension (PH) encompasses a set of heterogeneous progressive conditions characterised by increased pulmonary artery pressure, which, if left untreated, leads to right ventricular failure, causing substantial morbidity and, ultimately, premature death.[1] Fortunately, several PH-specific treatments were introduced over the past decades, resulting in considerable gains in terms of long-term patient survival.[2,3] Since then, research shifted towards more intense evaluation of functional capacity and quality of life to ensure effective, patient-centered management of this highly debilitating condition.[4,5] Disability due to PH is multifactorial, depending on factors such as decreased exercise capacity, functional limitation, compensatory physiological mechanisms, psychological impact of the disease, as well as drug adverse effects, and burden of treatment.[6]

Several types of instruments have been used in patients with PH to evaluate functionality, health-related quality of life and quality of life,[4,5] including general assessment questionnaires,[7-9] as well as disease-specific questionnaires.[10-15] Health-related quality of life (HRQOL) has also been evaluated as a prognostic factor and treatment goal in the clinical management of PH.[16] However, to our knowledge, no specific evaluation of functioning and disability in PH populations

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has been done using the standardised functioning and disability classification developed by the World Health Organisation (WHO), the International Classification of Functioning, Disability and Health (ICF).[17]

The ICF does not classify people, but rather interprets their characteristics, namely, body structures and functions, activities and participation, and the influences of the environment, which allows to properly describe functional states. Functioning or disability are considered as a result of a dynamic interaction between health conditions and contextual factors.[17] Using this framework is important, because, although functioning and disability are intercorrelated with HRQOL, this framework provides an objective measure of functioning (*i.e.*, objective ability to perform in a given life domain), while HRQOL assessments provide a subjective measure of well-being (*i.e.*, subjective feeling about the ability to perform in a given life domain).[18] ICF is operationalized through the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0), which is a generic instrument for assessing health status and disability across different cultures and settings.[18,19] WHODAS 2.0 has increasingly been used in clinical practice and described in the medical literature, and it is considered the leading standard measure of disability worldwide.[19] Although being a generic, standardised measure, its psychometric proprieties have been repeatedly validated in diverse populations, locations, and languages, which makes WHODAS 2.0 the tool of choice in comparing disability due to different disease conditions and makes it possible to monitor the impact of health-related interventions.[18,19]

This study aimed to characterise the degree of disability in a population of Portuguese PH patients based on the WHODAS 2.0, and to identify clinical correlates of disability. Additionally, the study purposed to explore the capacity of WHODAS 2.0 in predicting the clinical evolution of PH patients.

METHODS

Study design and population

This is a prospective, observational study of prevalent PH patients (confirmed through right heart catheterisation) followed at a single reference centre in the North of Portugal (Pulmonary Vascular Disease Unit of Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal); the centre is part of the European Reference Network for Rare or Low Prevalence Complex Diseases (ERN-LUNG), and covers a region with approximately 3.8 million adult population.

When attending a routine clinical visit, patients were consecutively invited to participate in the study. Patients were eligible to participate if they were ≥ 18 years old and able and willing to give their informed consent. Patients were excluded from the study if they were unable to complete the study data collection forms due to illiteracy or cognitive impairment, or if they were not able to comply with the study protocol, due to other medical conditions or personal circumstances. Patients with group 2 and 3 PH were excluded from the study.

All patients provided their written informed consent prior to enrolment. The study protocol and data collection instruments received favourable opinion by the Ethics Committee of Centro Hospitalar do Porto (Porto, Portugal) and were reviewed and approved by the Portuguese National Data Protection Commission.

Data collection

Data were collected by self-administering the Portuguese validated version of WHODAS 2.0 questionnaire during a scheduled routine clinical visit. Sociodemographic and disease-specific clinical measures, including haemodynamic ones, were retrieved from the clinical database collected by the dedicated PH software created at the Unit, PAHTool (Inovultus, Santa Maria da Feira, Portugal).

WHODAS 2.0

WHODAS 2.0 can be self-administered and captures the level of functioning in six domains of life: cognition, mobility, self-care, getting along, life activities (household and work) and participation. The 36-item Portuguese validated version of WHODAS 2.0 was used in this study.[20] WHODAS 2.0 scoring and interpretation were performed according to the WHODAS 2.0 manual.[18] The complex scoring method was used. This scoring consists of three essential steps:

- summing of recoded item scores within each domain;
- summing of all six domain scores;
- converting the summary score into a metric ranging from 0 to 100, in which 0 is no disability and 100 means full disability.

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD) or frequency (%). Differences in mean WHODAS scores for different subgroups were tested using one-way ANOVA/Kruskal-Wallis test. For the purposes of analysis, patients with group 1 and group 5 PH were grouped, since there were only three patients in group 5 and all patients received PH-specific treatment.

Bivariate correlation analysis correlating patients' demographic and clinical variables with WHODAS scores was conducted by using Spearman's Rank correlation coefficient (between quantitative variables) and by using point-biserial correlation (between quantitative variables and binary nominal variables). Then, multiple linear regression analysis was established only for the significant correlations to identify possible predictors for WHODAS scores. The method of selecting significant variables was the forward likelihood ratio (stepping method criteria: entry = 0.05; removal = 0.10), and no estimation problems were found. A dummy

variable technique was used to incorporate qualitative independent variables in the regression models.

For the variables measured at the end of the study: disease progression, functional class, 6-minute walking distance (6MWD), N-terminal pro b-type natriuretic peptide (NT-proBNP), and risk classification, prediction models based on WHODAS dimensions or WHODAS total score were established. For the first two variables, binary regression models were used. For the following two variables, linear multiple regression models were derived. For the last variable, an ordinal regression model was conducted (using the probit link function).

Statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, United States), and results were considered significant if $p < 0.05$.

RESULTS

Patient characteristics

Patient characteristics at baseline are summarised in Table 1. This was a prevalent, stable PH population, diagnosed through right heart catheterisation with a mean disease duration of approximately 6.8 years. Most participants were female (63.0%), and the mean age of the study population was 54.5 ± 16.2 years. The most frequent PH aetiologies were chronic thromboembolic pulmonary hypertension (CTEPH) (30.4%), idiopathic/heritable pulmonary arterial hypertension (I/HPAH) (17.4%), connective tissue diseases (CTD) (17.4%), and congenital heart diseases (CHD) (15.2%). For the purpose of analysis, aetiologies are from here on grouped as group 1 and 5 PH (69.6%) and group 4 PH (30.4%). Comorbidities were frequent, present in 67.4% of patients, with a mean of approximately two comorbidities per patient (range = 6; Q1 = 0; Q3 = 3).

Overall, this population showed PH disease markers indicative of low (26.0%), intermediate (54.3%) and high (19.5%) estimated 1-year mortality risk, according to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines risk assessment scale.[1] Most patients were in WHO functional classes I or II (71.7%), with a mean 6MWD of 415.1 ± 130.1 meters. Self-reported dyspnoea was referred by 54.3% of patients and self-reported fatigue by 39.1%. There was oxygen desaturation (94.0 ± 3.1 to 82.3 ± 9.2) during 6MWT and a 2-fold elevation NT-proBNP levels. PH-specific treatment was used in the vast majority of patients (84.8%), 50% of them in combination therapy, all through oral route (100% of treated patients); only 12.8% were under PH-specific treatment through parenteral route. Adjunctive treatment with oxygen (37.0%), diuretics (50.0%), and oral anticoagulants (60.9%) was frequent.

WHODAS 2.0 Disability scores

WHODAS 2.0 scores were indicative of mild to moderate disability for the domains of mobility (22.0 ± 23.2), life activities (23.7 ± 25.5), and participation in society (17.2 ± 15.9). For the domains of cognition (9.1 ± 14.1), self-care (8.3 ± 14.4), and interpersonal relationships (11.7 ± 15.7), scores were lower. Mean WHODAS 2.0 total score was 15.3 ± 15.2, reflecting the variability between the different domains and indicating only mild general disability in the studied population.

Figure 1 presents mean WHODAS 2.0 scores measured in the study population at baseline according to gender and PH risk group. Mean WHODAS 2.0 scores were generally proportional to the PH risk classification, with higher risk patients showing higher degrees of disability. Mean WHODAS 2.0 total score was 8.7 ± 9.0 for low-risk patients, 15.4 ± 14.9 for intermediate-risk patients, and 24.1 ± 19.2 for high-risk patient ($p = 0.150$). As for the different domains, higher risk patients generally showed numerically higher WHODAS 2.0 scores, but the differences only reached statistical significance for the interpersonal relationship domain ($p = 0.021$). Women did not show significantly different scores from men for any domain.

Clinical correlates of disability

In bivariate analysis (Table 2), WHO Functional class and Borg fatigue index were the variables that showed stronger correlations with all domains, as well as the total WHODAS 2.0 score (correlation generally > 0.5 or < -0.5). For the life activities domain, fatigue was also strongly correlated (0.512), whereas for the participation in society domain the Borg dyspnea index was also strongly correlated (0.571). The total WHODAS 2.0 score was, in addition, strongly correlated with years of schooling (-0.501), fatigue (0.515), and the Borg dyspnea index (0.561). Figures S1 e S2 (Appendix) show scatterplots for correlations between WHODAS 2.0 scores and 6MWD. The Appendix is available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=62

Multivariate analysis (Table 3) showed substantially different results for each WHODAS 2.0 domain. For the cognition domain, the significant variables were WHO functional class and pulse pressure (systolic minus diastolic blood pressure). For the mobility domain, the significant variables were WHO functional class and self-reported fatigue. For the self-care domain, only WHO functional class was a statistically significant variable. For the interpersonal relationship domain, the Borg fatigue index and NT-proBNP were the significant variables. For the life activities domain, self-reported fatigue was the significant variable. For the domain of participation in society, the years of schooling, the Borg fatigue index, and pulse pressure were significant variables. Overall, for the total WHODAS 2.0 score, only self-reported fatigue and WHO functional class were significant factors in multivariate analysis.

Disease progression

Table 4 presents the evolution of the main PH disease markers at the final study visit. Over a mean

Table 1. Sociodemographic and clinical characteristics of the study population at baseline.

Characteristics	PH patients (N = 46)
Female, n (%)	29 (63.0)
Age, years	54.5 ± 16.2
Marital status, n (%)	
Single/divorced/widowed	14 (30.4)
Married/cohabitation	32 (69.6)
Working status, n (%)	
Full-time	10 (21.7)
Retired/homemaker	25 (54.3)
Unemployed	11 (23.9)
Schooling, n (%)	
No formal education	6 (13.0)
Basic education (up to 9 years)	30 (65.2)
Secondary education (12 years)	6 (13.0)
University education	4 (8.7)
Disease duration, days	2,487.2 ± 3,199.9
PH aetiology, n (%)	
PAH	29 (63.0)
I/HPAH	8 (17.4)
CTD	8 (17.4)
CHD	7 (15.2)
PoPH	4 (8.7)
HIV	2 (4.3)
Other	3 (6.5)
Splenectomy	2 (4.3)
Sarcoidosis	1 (2.2)
CTEPH	14 (30.4)
Comorbidities, n (%)	31 (67.4)
Comorbidities number per patient	1.9 ± 1.8
Self-reported dyspnoea, n (%)	25 (54.3)
Self-reported fatigue, n (%)	18 (39.1)
WHO Functional class, n (%)	
I/II	33 (71.7)
III/IV	13 (28.3)
NT-proBNP, pg/mL	401.1 ± 477.9
6MWD, meters	415.1 ± 130.1
Borg (dyspnoea)	1.7 ± 2.6
Borg (fatigue)	2.8 ± 2.8
O_2Sat_bas, %	94.0 ± 3.1
O_2Sat_mn, %	82.3 ± 9.2
Delta O_2Sat	11.9 ± 7.8
SBP, mmHg	117.2 ± 20.2
DBP, mmHg	67.1 ± 13.2
Pulse pressure, mmHg	50.1 ± 13.9
Creatinine, mg/dL	0.9 ± 0.3
RAP, mmHg	7.9 ± 4.4
mPAP, mmHg	46.0 ± 15.9
CI, L/min/m^2	3.3 ± 1.1
PVR, Wood units	6.0 ± 3.4
PH risk classification, n (%)	
Low	12 (26.0)
Intermediate	25 (54.3)
High	9 (19.5)
Oxygen therapy, n (%)	17 (37.0)
Oral anticoagulants, n (%)	28 (60.9)
Diuretics, n (%)	23 (50.0)
PH-specific therapy, n (%)	39 (84.8)
Number of PH-specific drugs	1.5 ± 0.9
Oral route, n (%)	39 (84.8)
Parenteral route, n (%)	5 (10.9)
Other drugs, number	2.2 ± 2.2

Data displayed as mean ± standard deviation (SD), except when otherwise indicated. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; CTD: connective tissue diseases; CHD: congenital heart diseases; PoPH: portopulmonary hypertension; HIV: human immunodeficiency virus; CTEPH: chronic thromboembolic pulmonary hypertension; WHO: World Health Organization; NT-proBNP: N-terminal Pro b-type natriuretic peptide; 6MWD: 6-minute walking distance; SBP: systolic blood pressure; DBP: diastolic blood pressure; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; O2Sat_mn: minimum oxygen saturation; Sat_bas: baseline oxygen saturation.

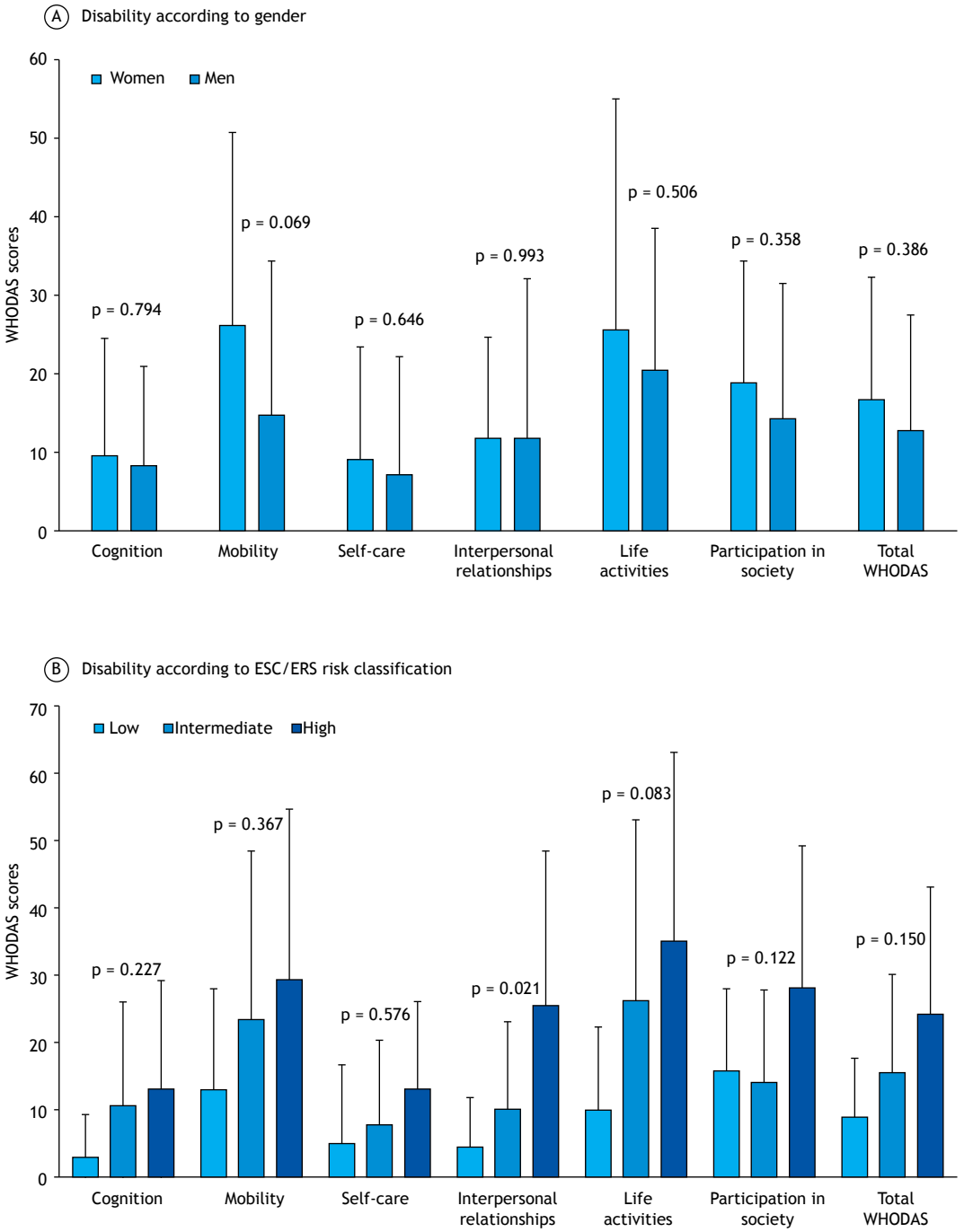

Figure 1. Mean World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores in the study population at baseline according to (A) gender and (B) pulmonary hypertension risk classification. Error bars represent standard deviations.

follow-up time of approximately 11 months, few patients (13.0%) showed disease progression. There was a slight improvement in WHO functional class, with the proportion of patients in functional classes I/II increasing from 71.7 to 76.1%. 6MWD also increased slightly from baseline to final visit (mean improvement of 5.6 ± 85.8 meters). Mean levels of NT-proBNP increased substantially from baseline to final visit, from a 2-fold elevation at baseline to a 3-fold elevation at final visit. The number of patients in intermediate and high risk slightly increased from 54.3 to 60.9% and from 19.5 to 23.9%, respectively.

Table 5 explores the association between baseline WHODAS 2.0 scores and patient evolution in terms of 6MWD and NT-proBNP levels at final visit. In bivariate analysis, 6MWD at final visit was strongly associated with

Table 2. Correlation results for the relationship between patient characteristics at baseline and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores.

	Cognition	Mobility	Self-care	Interpersonal relationship	Life activities	Participation in society	Total
Age, years	0.042	0.306*	0.182	0.371*	0.340*	0.148	0.405**
Schooling, years	-0.217	-0.400**	-0.308*	-0.458**	-0.452**	-0.411**	-0.501***
Working status	0.066	0.213	0.227	0.232	0.232	0.106	0.317*
PH aetiology	0.191	0.175	0.105	0.328*	0.295*	0.209	0.343*
Self-reported dyspnoea	0.207	0.146	0.175	0.341	0.337*	0.190	0.273
Self-reported fatigue	0.451**	0.540**	0.369*	0.222	0.512***	0.390**	0.515***
No							
Yes							
WHO Functional class	0.629***	0.591***	0.590***	0.598***	0.560***	0.596***	0.671***
I/II							
III/IV							
6MWD, meters	-0.389	-0.417**	-0.229	-0.349*	-0.393**	-0.212	-0.419**
Borg (dyspnoea)	0.293	0.467**	0.251	0.476**	0.424**	0.571***	0.561***
Borg (fatigue)	0.583***	0.627***	0.420**	0.598***	0.554***	0.699***	0.738***
Pulse pressure	-0.401**	-0.207	-0.400**	-0.260	-0.217	-0.298*	-0.233
Sat_bas, mmHg	-0.074	-0.044	-0.175	-0.206	-0.326*	-0.035	-0.338
Creatinine (mg/dL)	0.200	0.052	0.029	0.210	0.340*	0.146	0.243
NT-proBNP, pg/mL	0.231	0.111	0.193	0.405**	0.148	0.192	0.272
CI, L/min/m^2	-0.198	0.068	-0.044	-0.394*	-0.257	-0.074	-0.167
PVR, Wood units	0.091	-0.140	0.025	0.159	0.169	0.134	0.025
Oxygen Therapy	0.191	0.306*	0.290*	0.336*	0.295*	0.227	0.309*
Risk classification[a]	0.220	0.211	0.154	0.399**	0.327*	0.144	0.283
Low							
Intermediate							
High							

PH: pulmonary hypertension; WHO: World Health Organization; 6MWD: 6-minute walk distance test; Sat_bas: basal oxygen saturation; NT-proBNP: N-terminal pro b-type natriuretic peptide; CI: cardiac index; PVR: pulmonary vascular resistance. For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: gender, marital status, disease duration, comorbidities, number of comorbidities, body mass index (BMI), basal heart rate (HR_Bas), maximum heart rate (HR_Max), maximum - basal heart rate (DeltaHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), minimum oxygen saturation (Sat_min), basal - minimum oxygen saturation (DeltaSat), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), haemoglobin, haematocrit, oral anticoagulants, diuretics, PH specific therapy, number of PH specific drugs, PH specific oral route, PH specific parenteral route, other drugs, number of other drugs. Correlation coefficients calculated using Spearman's rank (quantitative *vs.* quantitative variables) or point-biserial (quantitative *vs.* categorical). [a]Estimated risk of 1-year mortality, according to the 2015 ESC/ERS guidelines risk assessment scale. *p < 0.05; **p < 0.01; ***p < 0.001. Correlations with p < 0.01 are presented in bold.

all WHODAS 2.0 dimensions except cognition, whereas NT-proBNP levels only showed a weak association with the cognition, mobility, and life activities domains. In multivariate analysis, 6MWD at final visit was significantly associated with the interpersonal relationships domains, whereas NT-proBNP was significantly associated with the mobility and self-care domains.

The relationship between WHODAS 2.0 scores and WHO functional class and occurrence of disease progression was assessed through binary logistic regression, with no significant results for any of WHODAS domains. Nonetheless, total WHODAS 2.0 score at baseline was significantly associated with WHO functional class at final visit (*odds ratio*—OR: 1.124 [1.051–1.203; p < 0.001]).

Lastly, the predictive power of WHODAS 2.0 scores in terms of risk classification at last visit was assessed through ordinal regression. This analysis revealed a statistically significantly association only for the mobility domain (estimate: 3.919 [0.746–7.092]; p < 0.05). The correct overall classification percentage between the observed and the predicted categories was 66.7%, with the following distribution of risk: low (14.2%), intermediate (89.3%), and high (54.5%).

DISCUSSION

This study provides, to our knowledge, the first characterisation of disability in patients with PH based on the WHODAS 2.0 standardised assessment instrument. Using this type of tool to access disability across varied populations—both in terms of location and diseases states—, it can provide valuable insights in establishing better clinical care and improving overall public health. WHODAS 2.0 is particularly useful for these types of

Table 3. Multivariate linear regression (β coefficients and the correspondent 95%CI) for the relationship between patient characteristics at baseline and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores.

	Cognition	Mobility	Self-care	Interpersonal relationship	Life activities	Participation in society	Total
Schooling, years						-5.4 [-10.4;-0.3]	
Self-reported fatigue		-			-		-
No		18.7			36.3		9.2
Yes		[8.3;29.0]			[20.8;51.8]		[2.7;15.8]
WHO Functional class	-	-	-				-
I/II	19.7	24.5	15.3				18.1
III/IV	[12.8;26.7]	[13.2;35.9]	[8.2;22.3]				[10.9;25.2]
Borg (fatigue)				2.7 [1.6;3.8]		2.58 [1.23;3.94]	
Pulse pressure	-0.23 [-0.45;-0.01]					-0.37 [-0.63;-0.11]	
Creatinine (mg/dL)					34.3 [12.5;56.1]		
NT-proBNP, pg/mL				0.01 [0.00;0.01]			
Constant	15.1 [3.5;26.8]	7.2 [1.3;13.1]				34.2 [16.7;51.8]	
R^2 Ajustated	0.477	0.534	0.301	0.445	0.483	0.454	0.539

CI: cardiac index; WHO: World Health Organisation; NT-proBNP: N-terminal pro b-type natriuretic peptide. For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: age, gender, marital status, working status, pulmonary hypertension (PH) aetiology, disease duration, self-reported dyspnoea, comorbidities, number of comorbidities, body mass index (BMI), 6-minute walk distance test (6MWD), Borg (dyspnoea), basal heart rate (HR_Bas), maximum heart rate (HR_Max), maximum - Basal heart rate (DeltaHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), minimum oxygen saturation (Sat_min), basal oxygen saturation (Sat_bas), basal - minimum oxygen saturation (DeltaSat), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), haemoglobin, haematocrit, CI, pulmonary vascular resistance (PVR), oxygen therapy, oral anticoagulants, duretics, PH specific therapy, number of PH specific drugs, PH specific oral route, PH specific parenteral route, other drugs, number of other drugs, ESC/ERC risk classification. R^2 Adjusted represents the proportion of variability explained by the proposed model. Relationships with $p < 0.01$ are presented in bold.

assessments, because it is based on the biopsychological model of functioning and disability defined by the ICF, which takes into account the degree on disability actually perceived by the individuals and, therefore, constitutes a better basis for targeted therapeutic interventions and public health policies. Also, being a standardized tool, it allows comparative studies with other health conditions and in different contexts.

The population of PH patients in this study showed low to intermediate PH disease severity, despite a disease duration of approximately seven years. Low to intermediate disease severity is reflected in the degree of disability observed in the study population according to WHODAS 2.0 scores, which showed mostly mild disability for individual WHODAS 2.0 domains and WHODAS 2.0 total score (15.3 ± 15.2). The domains of mobility and life activities were the ones in which patients showed more disability, which could be expected given the impairments in exercise capacity that characterise PH.[1]

The degree of disability observed in this population is markedly lower than previous reports in populations with cardiorespiratory conditions with somewhat comparable disease manifestations.[19] Racca et al. assessed disability in a population of ischaemic heart disease patients, reaching a mean total WHODAS 2.0 score of approximately 24 points (with a score of approximately 50 for the life activities domain).[21] Pedro-Cuesta et al. assessed disability in a population of patients with chronic obstructive pulmonary disease, chronic heart failure, or stroke and found total WHODAS 2.0 scores of 26, 38, and 28, respectively.[22] In a large population of patients with chronic diseases—including patients with ischemic heart disease—, Garin et al. reported a total WHODAS 2.0 score of 24.8 ± 19.3, with scores in the life activities domain of 37.[23] The authors provided, however, estimates of disability according to disease severity, and our results are, actually, comparable to those of patients with ischaemic heart disease of mild to moderate severity.[23]

These findings support the assertion that the low degree of disability observed in our study population can be explained by the disease severity endured by the patients. We hypothesise that the relatively mild disability in the context of this highly debilitating and progressive disease is associated with the type of clinical management provided to these patients, which are followed in a highly-specialised PH treatment unit, without difficulties in accessing approved PH-specific drugs. Importantly, 84.8% of patients were under treatment with PH-specific drugs, 59% in combination therapy, which is expected to result in better disease

control and substantially fewer disease manifestations, thus vastly improving overall patient functioning.

The main baseline variables associated with disability measured through WHODAS 2.0 in this study cohort were WHO functional class, fatigue (and Borg fatigue index), dyspnoea (and Borg dyspnoea index), 6MWD, and NT-proBNP. These results are largely in agreement with previous studies assessing general health status and health-related quality of life in PH populations.[5] Several studies identified WHO functional class,[24-28] fatigue,[24,25] and dyspnoea[24,25] to be highly associated with overall health status and health-related quality of life. Additionally, there was an important negative correlation between education and scores for the domain of participation in society; this effect is, however, likely associated with the social involvement of participants in their communities, irrespective of PH.

Several variables that are usually important for the clinical management of PH patients showed only weak or even no correlation with disability scores. Age and PH aetiology did not reach statistical significance in the multivariate regression model, which indicates that other variables are more important in a multivariate context. Similarly, PH risk classification showed sporadic significant correlations with disability scores in bivariate analysis, but it was not considered a significant factor in the multivariate model. On the other hand, disease duration, PH-specific treatment, and the presence of comorbidities did not even show significant correlations in bivariate analysis. These results could potentially be explained by reduced variability in this relatively small population.

When using WHODAS 2.0 scores at baseline to predict evolution of PH markers over the 11-month period of the study, disability scores were only robustly predictive of 6MWD and WHO functional class evolution. There were a strong negative correlation between the mobility domain and 6MWD at final visit and a strong positive correlation between WHODAS 2.0 total score and WHO functional class at last visit, as would also be expected in both cases.

Some limitations of this study should be considered. The study had a moderate sample size (N = 46) even in the context of PH, which is an infrequent

Table 4. Clinical characteristics of the study population at final visit (end of study).

Characteristics	PH patients (n = 46)
Follow-up time, days	337.4 ± 140.1
Disease progression, n (%)	
Yes	6 (13.0)
No	40 (87.0)
WHO Functional class, n (%)	
I/II	35 (76.1)
III/IV	11 (23.9)
6MWD, meters	412.7 ±134.8
NT-proBNP, pg/mL	585.6 ± 1046.3
Risk classification, n (%)	
Low	7 (15.2)
Intermediate	28 (60.9)
High	11 (23.9)

PH: Pulmonary hypertension; WHO: World Health Organisation; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal pro b-type natriuretic peptide. Data displayed as mean ± standard deviation (SD), except when otherwise indicated.

Table 5. Correlation and multivariate linear regression for the relationship between World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores and patient evolution measured at final visit (end of study).

	6MWD		NT-proBNP	
WHODAS 2.0 Dimensions	Correlation coefficient	Linear regression β [95%CI]	Correlation coefficient	Linear regression β [95%CI]
Cognition	-0.299	1.82 [-1.05;4.70]	0.351*	20.80 [3.51;45.11]
Mobility	-0.616***	-3.48** [-5.95;-1.01]	0.361*	36.88*** [16.42;57.34]
Self-care	-0.527***	0.420 [-3.11;3.95]	-0.075	-65.75*** [-93.22;-38.29]
Interpersonal relationship	-0.599***	-5.19*** [-7.97;-2.40]	0.207	14.32 [-8.46;37.11]
Life activities	-0.508***	-0.909 [-2.86;1.04]	0.300*	-4.79 [-21.28;11.70]
Participation in society	-0.450***	3.13 [-0.42;6.67]	0.267	2.35 [-27.69;32.39]
Constant	NA	494.5*** [449.7;539.2]	NA	38.0 [-338.3;414.3]
R^2 Ajustated	NA	0.498	NA	0.401

6MWD: 6-minute walk distance test; NT-proBNP: N-terminal pro b-type natriuretic peptide: NA: not applicable; 95%CI: confidence interval of 95%.For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: Delta_6MWD; Delta NT-proBNP. Correlation coefficients calculated using Spearman's rank (quantitative *vs.* quantitative variables) or point-biserial (quantitative *vs.* categorical). R^2 Adjusted represents the proportion of variability explained by the proposed model. *p < 0.05; **p < 0.01; ***p < 0.001.

condition. The sample was compounded with only a small number of patients with severe forms of PH (19.5%) that are expected to show substantially higher degrees of disability, which limits comparisons with previous reports from populations with higher levels of disability. Further studies should focus on assessing more heterogeneous PH populations in terms of disease severity. Additionally, the study had a relatively short mean follow-up time, which could hinder the assessment of the predictive value of baseline WHODAS 2.0 scores, since few events of interest occurred throughout the period of the study.

In conclusion, this population of Portuguese PH patients shows mild disability as assessed through WHODAS 2.0, which can be associated with low to intermediate disease severity. Higher degree of disability is found in the domains of mobility and life activities. The main clinical correlates of disability in this population are WHO functional class, fatigue, and dyspnoea. WHODAS 2.0 scores at baseline predict 6MWD and WHO functional class over an 11-month follow-up period.

This study was the first one to assess disability in PH using WHODAS 2.0. Further studies should apply this scale to larger PH populations with suitable representations of more severe forms of PH.

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ORIGINAL ARTICLE

Evaluating the extremely elderly at a pulmonary function clinic for the diagnosis of respiratory disease: frequency and technical quality of spirometry

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ABSTRACT

Objective: To determine the frequency of spirometry in elderly people, by age group, at a pulmonary function clinic, to assess the quality of spirometry in the extremely elderly, and to determine whether chronological age influences the quality of spirometry. **Methods:** This was a cross-sectional retrospective study evaluating information (spirometry findings and respiratory questionnaire results) obtained from the database of a pulmonary function clinic in the city of Aracaju, Brazil, for the period from January of 2012 to April of 2017. In the sample as a whole, we determined the total number of spirometry tests performed, and the frequency of the tests in individuals ≥ 60 years of age, ≥ 65 years of age, and by decade of age, from age 60 onward. In the extremely elderly, we evaluated the quality of spirometry using criteria of acceptability and reproducibility, as well as examining the variables that can influence that quality, such a cognitive deficit. **Results:** The sample comprised a total of 4,126 spirometry tests. Of those, 961 (23.30%), 864 (20.94%), 102 (2.47%), and 26 (0.63%) were performed in individuals ≥ 60, ≥ 65, ≥ 86, and ≥ 90 years of age (defined as extreme old age), respectively. In the extremely elderly, the criteria for acceptability and reproducibility were met in 88% and 60% of the spirometry tests (95% **CI:** 75.26-100.00 and 40.80-79.20), respectively. The cognitive deficit had a negative effect on acceptability and reproducibility ($p \leq 0.015$ and $p \leq 0.007$, respectively). **Conclusions:** A significant number of elderly individuals undergo spirometry, especially at ≥ 85 years of age, and the majority of such individuals are able to perform the test in a satisfactory manner, despite their advanced age. However, a cognitive deficit could have a negative effect on the quality of spirometry.

Keywords: Spirometry; Aging; Aged, 80 and over.

INTRODUCTION

In Brazil and worldwide, the elderly population has grown because of decreased birth rates and a significantly increased lifespan.[1-3] The elderly population is estimated to reach nearly 2 billion by 2050, that is, it will represent approximately 22% of the world population.[1,4] The World Health Organization defines elderly as persons ≥ 60 years of age in developing countries, such as Brazil, and as persons ≥ 65 years of age in developed countries.[1] Aging can be classified into four stages: middle age (45-59 years); old age (60-74 years); old-old age (75-89 years); and extreme old age (90 years and over).[5]

The prevalence of respiratory diseases increases in the elderly population, and respiratory symptoms, such as cough and dyspnea, may be associated with non-respiratory comorbidities, such as heart diseases, muscle weakness, anemia, and lack of physical fitness, all of which may confuse the correct diagnosis.[6,7] Spirometry is the most available and most widely used pulmonary function test in clinical practice, and it should be a part of the evaluation of patients with respiratory symptoms or suspected respiratory disease, as well as of the treatment follow-up of various respiratory diseases, especially obstructive diseases, such as asthma and COPD.[8-11] However, spirometry is not routinely used by geriatricians, and most studies with spirometry involve a limited number of elderly individuals.[6,11-13] The question remains, even among geriatricians, as to whether age is a limiting factor in the elderly's ability to perform spirometry in a satisfactory manner.[6,12,14,15]

The objective of the present study was to determine the frequency and proportion of spirometry in an elderly population, by age group, at a pulmonary function clinic. We also aimed to assess the quality of spirometry results in the extremely elderly and to determine whether chronological age influences the quality of spirometry.

METHODS

This was a cross-sectional retrospective study conducted at *Universidade Tiradentes*, located in the city of Aracaju, Brazil. The sample data (spirometry findings and respiratory questionnaire results) were obtained from the database of a pulmonary function clinic, located in

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Aracaju, for the period from January of 2012 to April of 2017. The study was approved by the Research Ethics Committee of *Universidade Tiradentes* (CAAE no. 67734717.2.0000.5371).

All spirometry tests were performed in the same room using the same spirometer with a pneumotachograph (Microlab 3500; Micro Medical Ltd., Rochester, England) connected to a computer where the spirometry data were stored. The stored data for each test were examined and evaluated individually regarding flow-volume and volume-time curves, as well as regarding conventional spirometric variables: FVC, FEV_1, FEV_1/FVC ratio, PEF, and mid-expiratory flows, the results of which were expressed as liters and as a percentage of normal values according to the equations proposed by Crapo et al.[16] (for the population ≥ 87 years of age) or the equations proposed by Pereira et al.[17] (for the population ≤ 86 years of age).

At least three curves were performed. Spirometry tests were performed in accordance with the technical standards and the acceptability and reproducibility criteria proposed by the Brazilian Thoracic Association,[10] as were assessments of the quality of spirometry and spirometry interpretations. The same pulmonologist, who is certified in spirometry, interpreted the spirometry results.

Curves were accepted if they met the following criteria: abrupt start and absence of hesitation; a PEF variation of less than 10% of the highest PEF obtained or 0.5 L/s (whichever was greater); a back-extrapolated volume of less than 5% of FVC or 150 mL (whichever was greater); a test duration of 6 s or an end-of-test plateau of 1 s on the volume-time curve; and no patient discomfort. In addition, cough in the first second of the maneuver, glottic closure, leak, and obstructed mouthpiece were criteria for rejection.[10,18]

The quality of spirometry was determined by assessing spirometry curves (flow-volume and volume-time curves), number of maneuvers performed, and values for spirometric variables. The quality of spirometry was graded as follows[10]:

- A: at least two acceptable maneuvers in eight attempts, with the two highest FVC values and the two highest FEV_1 values differing by 150 mL or less and with PEF being less than 10% or 500 mL (whichever was greater)
- B: at least two acceptable maneuvers with the two highest FVC values and the two highest FEV_1 values being between 150 and 200 mL or with PEF being less than 15%
- C: only one acceptable maneuver, or more than one acceptable maneuver, but with an FEV_1 variation of more than 200 mL
- D: no acceptable tests, no possibility of interpretation

The acceptability criteria included the parameters of quality A, B, and C tests, and the reproducibility criteria included those of quality A and B tests.

The standardized respiratory questionnaire used in spirometry assessed demographic and anthropometric factors; respiratory symptoms; smoking status; comorbidities; history of lung and heart disease; occupational history; history of surgery and intubation; medications in use; clinical indication; and identification information of the physician who ordered the test. In the absence of adequate data on patient comorbidities from that respiratory questionnaire, attending physicians were asked to review medical records.

In order to statistically analyze the influence of comorbidities on the quality of spirometry, we subdivided comorbidities into five groups on the basis of the most impaired organ system: cognitive deficit; cerebrovascular disease without cognitive deficit; cardiovascular disease; lung disease; and others. Some patients belonged to more than one group because they had more than one type of comorbidity.

In the first phase of the study, we determined the total number of spirometry tests performed during the study period, regardless of patient chronological age, and the frequency of spirometry in individuals ≥ 60 years of age, in those ≥ 65 years of age, and by decade of age, from age 60 onward. Subsequently, we determined the total number of individuals ≥ 86 years, by gender, because the reference equation used to calculate the new values for forced spirometry in Brazil is limited to age 86.[17]

In that first phase, we considered all spirometry tests performed, regardless of the fact that a given patient performed more than one test during the study period, taking only chronological age at the time of spirometry into account. In a second phase of the study, we selected and included patients ≥ 90 years of age and excluded those < 90 years of age. In order to assess the quality of spirometry, we considered only the first spirometry test performed by each patient.

Statistical analysis was performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were described as means and standard deviation, and categorical variables were expressed as absolute and relative frequencies. In order to determine whether demographic and comorbidity variables were significantly associated with the quality of spirometry, we used the chi-square test or Fisher's exact test to compare categorical data, and the Student's t-test for independent samples to compare numerical variables. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

During the study period, a total of 4,126 spirometry tests were performed in individuals of various age groups (from 6 to 97 years of age). Of those tests, 961 (23.30%) and 864 (20.94%) were performed in individuals ≥ 60 and ≥ 65 years of age, respectively. Analysis by decade of age, from age 60 onward, revealed that 211 spirometry tests (5.11%) were performed in individuals aged 60-69 years; 432 (10.47%) were performed in those aged 70-79 years; 292 (7.08%) were performed in those aged 80-89 years; and 26

(0.63%) were performed in those aged ≥ 90 years. In the sample as a whole, 102 (2.47%) tests were performed in individuals ≥ 86 years of age, of whom 67 (1.62%) were women and 35 (0.85%) were men (Figure 1).

When assessing the quality of the 26 spirometry tests of individuals ≥ 90 years of age (defined as extreme old age), we excluded 1 because it belonged to a patient who performed 2 tests, that is, we selected for the study the spirometry tests of 25 patients who were aged 90-97 years, mean age of 92.12 ± 2.22 years (95% CI: 91.20-93.04), and were predominantly female (18/25; 72%).

Table 1 presents the demographic and anthropometric characteristics, comorbidities, and smoking status of the patients ≥ 90 years of age (n = 25). Some patients had one or more comorbidities. Patient distribution by comorbidity group was as follows: 10 patients with lung disease (7 with asthma, 4 with COPD, and 1 with asthma and COPD); 17 patients with cardiovascular disease (systemic arterial hypertension, arrhythmias, and/or dyslipidemia); 4 patients with cerebrovascular disease without cognitive deficit (stroke sequela); 7 patients with cerebrovascular disease with cognitive deficit (Alzheimer's disease and other dementia); and 5 patients with other comorbidities (hypothyroidism, hearing deficit, diabetes mellitus, anxiety, and/or depression). For those 25 patients, spirometry was ordered by pulmonologists, in 21 (84%); by cardiologists, in 3 (12%); and by general practitioners, in 1 (4%; Figure 2).

The acceptability criteria were met in 22 of the 25 spirometry tests (88%; 95% CI: 75.26-100.00), with 13 tests being graded quality A (52%; 95% CI: 32.42-71.58); 2 being graded quality B (8%; 95% CI: 0.00-18.63); 7 being graded quality C (28%; 95% CI: 10.40-45.60); and 3 being graded quality D (12%; 95% CI: 0.00-24.74; Figure 3 and 4). The reproducibility criteria were met in 15 of the 25 spirometry tests (60%; quality A and B tests; 95% CI: 40.80-79.20) and were not met in 10 (40%; quality C and D tests; Figure 4).

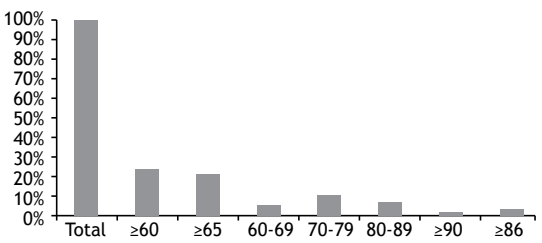

Figure 1. Distribution of spirometry tests (N = 4,126) performed during the study period, by age group.

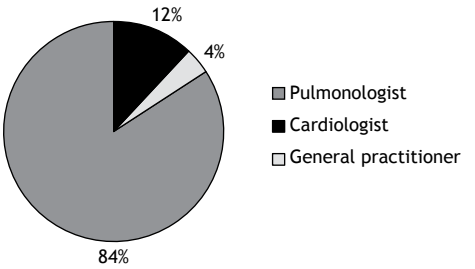

Figure 2. Specialty of the physician who ordered spirometry for individuals ≥ 90 years of age.

Table 1. Demographic and anthropometric characteristics, smoking status, and comorbidities in individuals ≥ 90 years of age.[a]

Variable	Age ≥ 90 years (n = 25)	95% CI
Female gender	18 (72)	
Age, years	92.12 ± 2.22	91.2-93.04
Height, m	1.48 ± 0.07	1.45-1.51
BMI, kg/m^2	27.74 ± 5.46	25.49-30.00
Weight, kg	60.64 ± 10.92	56.13-65.15
Smoking status		
Nonsmoker	21 (84)	
Former smoker	3 (12)	
Smoker	1 (4)	
Comorbidities[b]		
Asthma	7 (28)	
COPD	4 (16)	
SAH	14 (56)	
Dyslipidemia	7 (28)	
OSA	5 (20)	
Cardiac arrhythmia	4 (16)	
Cerebrovascular disease	4 (16)	
Cognitive deficit	7 (28)	
Other comorbidities[c]	5 (20)	

BMI: body mass index; SAH: systemic arterial hypertension; and OSA: obstructive sleep apnea. [a]Values expressed as n (%) or as mean ± SD. [b]Some patients had one or more comorbidities. [c]Hypothyroidism, hearing deficit, diabetes mellitus, anxiety, and/or depression.

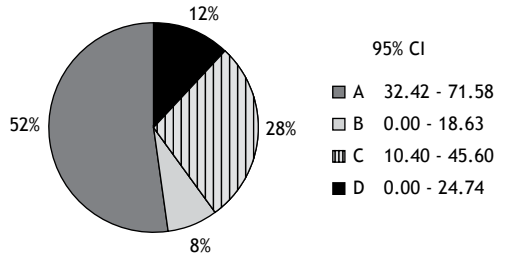

Figure 3. Spirometry quality grading in individuals ≥ 90 years of age. Adapted from the Brazilian Thoracic Association.[10]

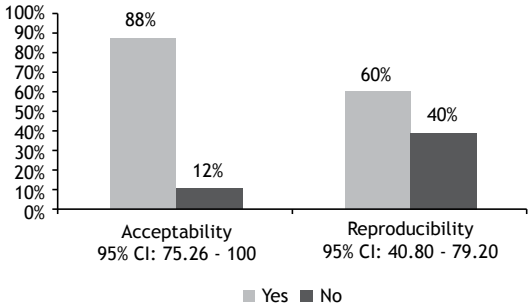

Figure 4. Acceptability and reproducibility of spirometry in individuals ≥ 90 years of age. Adapted from the Brazilian Thoracic Association.[10]

The spirometry tests that met the acceptability criteria (quality A, B, and C tests) were eligible for interpretation. The most common errors that had a negative effect on the quality (acceptability and/or reproducibility) of spirometry were as follows: submaximal effort, in 14 tests (56%); expiratory time of < 3 s and no plateau in the last second, in 7 (28%); no plateau in the last second, in 7 (28%); abrupt termination of expiration, in 7 (28%); cough, in 9 (36%); and leak, in 3 (12%). Some spirometry tests had more than one error, which explains why the total proportion of errors was greater than 100%.

The variables gender, age, body mass index (BMI), and comorbidity group were not found to influence the quality of spirometry, except for cognitive deficit, which had a negative effect on the quality of spirometry in terms of acceptability and reproducibility ($p \leq 0.015$ and $p \leq 0.007$, respectively), whereas lung disease showed the highest reproducibility ($p \leq 0.018$). The other variables (gender, age, and BMI) showed no significant differences (Table 2).

DISCUSSION

The elderly population is growing substantially worldwide.[1] By 2025, Brazil will rank 6th among the countries with the greatest number of elderly individuals in the world, with a high proportion of extremely elderly individuals (from 394,000 in 2010 to an estimated nearly 3.5 million in 2050).[3]

Although spirometry is practical and important to assessing pulmonary function, there have been few studies involving the elderly.[11] In the present study, we found that a significant number of elderly individuals attended the pulmonary function clinic on an outpatient basis. Of all spirometry tests performed, 961 (23.30%) were performed in individuals ≥ 60 years of age, 864 (20.94%) were performed in individuals ≥ 65 years of age, and 102 (2.47%) were performed in individuals ≥ 86 years of age.

When we analyzed reference equations for spirometry all over the world, we found few data on the elderly, and the existing data are based on relatively small, non-representative samples.[11,19-24] In Brazil, the equations proposed by Pereira et al.[17] in 2007 were derived in a sample of men and women up to 86 and 85 years of age, respectively, with a small number of patients over 75 years of age. In 2017, Rufino et al.[22] included patients up to 80 years of age in their sample, claiming that the average life expectancy in Brazil was 74 years. In 2012, the Global Lung Function Initiative,[11] endorsed by the European Respiratory Society, carried out a study that presented multi-ethnic reference equations for spirometry on the basis of 97,759 records of individuals who were aged 3-95 years (females, 55.3%) from 33 countries in five continents. In that sample, 0.8% of the individuals were ≥ 80 years of age, 0.24% were > 85 years of age, and only 0.035% were > 90 years of age. Those authors underscore the limitations of the predicted values for individuals > 75 years of age and suggest that these values be interpreted with caution.[11]

Given the estimated increasing number of extremely elderly individuals in the coming decades, the extremely elderly represent a specific group and a new challenge requiring study from a health standpoint, especially with regard to the respiratory system. We showed that 26 (0.63%) of the spirometry tests in our sample were performed in extremely elderly individuals, most of whom were women (72%). We found no previous research focusing exclusively on the extremely elderly, and existing studies on the elderly do not specify how many patients were over 90 years of age, making a proper comparison between those studies and ours difficult.[6,12-15,23,24]

Aging is accompanied by changes in all organ systems, either due to senescence or to the presence of a larger number of comorbidities. For this reason, the ability of elderly individuals to understand the phases of spirometry, coordinate their performance, and make the effort required to obtain reliable measures is questionable.[6,24,25] Approximately 15% of elderly individuals will not cooperate in performing spirometry.[10] Spirometry is not routinely used by geriatricians because the question remains as to whether age would be a limiting factor to performing spirometry adequately.[6,12,15]

Our study underscores the fact that spirometry was ordered basically by pulmonologists and cardiologists, although the patients in our sample were followed by geriatricians. This agrees with data in the literature that indicate that spirometry is not widely used in

Table 2. Determination of variables that can influence the acceptability and reproducibility of spirometry in the extremely elderly.[a,b]

Variable	Acceptability criteria			Reproducibility criteria		
	ABC (n = 22)	D (n = 3)	p	AB (n = 15)	CD (n = 10)	p
Female gender	16 (72.7)	2 (66.7)		10 (66.7)	8 (80.0)	
Comorbidity group[c,*]						
Lung disease	10 (45.5)	0 (0.0)	0.250	9 (60.0)	1 (10.0)	0.018
Cardiovascular disease	16 (72.7)	1 (33.3)	0.230	10 (66.7)	7 (70.0)	0.230
Cognitive deficit	4 (18.2)	3 (100.0)	0.015	1 (6.7)	6 (60.0)	0.007
Cerebrovascular disease	3 (13.6)	1 (33.3)	0.422	1 (6.7)	3 (30.0)	0.267
Others[d]	5 (22.7)	0 (0.0)	1.000	4 (26.7)	1 (10.0)	0.615
Age**	91.86 ± 2.17	94.00 ± 2.00	0.120	92.20 ± 2.43	92.00 ± 2.00	0.831
BMI**	27.80 ± 5.74	27.33 ± 3.44	0.890	28.21 ± 6.41	27.04 ± 3.83	0.608

IMC: body mass index. [a]Adapted from the Brazilian Thoracic Association.[10] [b]Values expressed as n (%) or as mean ± SD. [c]Some patients had one or more comorbidities. [d]Hypothyroidism, hearing deficit, diabetes mellitus, anxiety, and/or depression. *Fisher's exact test.**Student's t-test for independent samples.

geriatric practice, which leads to a limited number of spirometry results.

Our results showed that the criteria for acceptability and reproducibility were met in 88% and 60% of the spirometry tests, respectively, and that only 12% of the tests were excluded because of poor technique, which was significantly correlated with cognitive deficit. We also showed that age, gender, BMI, and comorbidities other than cognitive deficit did not interfere with the quality of spirometry.

A study[6] conducted with a sample of 715 individuals ≥ 65 years of age reported that 81.50% of the spirometry tests were accepted and 18.2% were excluded because of poor technique. Age, BMI, and presence of depression did not influence the quality of the test; however, cognitive impairment and a low level of education had a negative effect on the quality of spirometry.

Sherman et al.[12] evaluated 65 individuals ≥ 65 years of age (mean age, 75 years) and reported that 8 individuals (12.3%) were unable to perform spirometry and 18 (31.6%) did not meet the reproducibility criteria. Those authors suggest that the vast majority of elderly individuals are able to perform spirometry with adequate technique, and that elderly individuals who are unable to perform it may have impaired cognitive function.

A retrospective study[14] that assessed the quality of spirometry and DLCO testing by comparing 150 individuals ≥ 80 years of age (elderly group) with 178 adults aged 40-50 years (control group) reported that 139 (92.6%) of the elderly group and 163 (91.5%) of the control group spirometry tests met all acceptability and reproducibility criteria.

A study of elderly individuals ≥ 65 years of age who had obstructive disease (asthma and/or COPD) reported that cognitive impairment, shorter six-minute walk distances, and lower levels of education were independent risk factors for lower spirometry acceptability rates, whereas male gender and age were risk factors for poorer reproducibility of FEV_1.[15] In addition, previous studies that used the Mini-Mental State Examination have shown that cognitive deficit has a negative effect on the quality of spirometry.[13,26] The findings of the aforementioned studies are in agreement with those of our research, which showed that cognitive deficit had a negative effect on performing spirometry, and that chronological age did not interfere with the quality of spirometry. Chronological age does not always correspond to biological age; therefore, we must encourage active and healthy aging.

The limitations of the present study include the fact that it was a retrospective study and that the Mini-Mental State Examination was not used to assess the degree of cognitive deficit.

In conclusion, the present study calls attention to the fact that currently a significant number of elderly individuals undergo spirometry, especially at ≥ 85 years of age, and that the majority of such individuals are able to perform the test in a satisfactory manner. Age does not seem to be a limiting factor to performing spirometry, nor does extreme old age influence the quality of the test. However, cognitive deficit has a negative effect on the quality of spirometry. Therefore, spirometry can and should be used as a test to assess and control respiratory diseases in the extremely elderly, and its use should be disseminated and encouraged in geriatric practice.

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Pulmonary arteriovenous malformations: diagnostic and treatment characteristics

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ABSTRACT

Objective: To present a case series of pulmonary arteriovenous malformations (PAVMs), describing the main clinical findings, the number/location of pulmonary vascular abnormalities, the clinical complications, and the treatment administered. **Methods:** This was a retrospective observational study evaluating patients with PAVM divided into two groups: hereditary hemorrhagic telangiectasia (HHT); and idiopathic PAVM (iPAVM). **Results:** A total of 41 patients were selected for inclusion, but only 33 had PAVMs. After clinical evaluation, 27 and 6 were diagnosed with HHT and iPAVM, respectively. In the HHT group, the mean age was 49.6 years and 88.9% were female. In that group, 4 patients had an SpO_2 of < 90% and the most common clinical finding was epistaxis. In the iPAVM group, the mean age was 48.1 years and 83.3% were female. In that group, 3 patients had an SpO_2 of < 90%. Computed tomographic pulmonary angiography showed that most of the PAVMs were in the lower lobes: 56.4% in the HHT group and 85.7% in the iPAVM group. Embolization was performed in 23 patients (in both groups). At this writing, 10 patients are scheduled to undergo the procedure. One of the patients who underwent embolization was subsequently referred for pulmonary resection. **Conclusions:** In both of the PAVM groups, there was a predominance of women and of fistulas located in the lower lobes. Few of the patients had respiratory symptoms, and most had an SpO_2 > 90%. The treatment chosen for all patients was percutaneous transcatheter embolization.

Keywords: Telangiectasia, hereditary hemorrhagic; Arteriovenous malformations/diagnosis; Arteriovenous malformations/therapy.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are abnormal direct connections between a pulmonary artery and a pulmonary vein,[1] presenting with a variety of clinical manifestations. A right-to-left shunt, bypassing the capillary bed, compromises oxygenation and can lead to hypoxemia.[2] Patients with PAVMs are prone to infections (including cerebral, hepatic, and splenic abscesses), as well as ischemic stroke, which are due to abnormal vascular communications bypassing the filtering capacity of the capillary bed and allowing bacteria and thrombi to pass directly from the venous to the arterial blood.

One of the most common causes of PAVM is hereditary hemorrhagic telangiectasia (HHT),[3,4] which is also known as Osler-Weber-Rendu syndrome. An autosomal dominant disorder that is globally distributed, HHT has an estimated prevalence of 1:5,000 and is characterized by epistaxis and telangiectasia of different parts of the body, sometimes being accompanied by cerebral arteriovenous malformations (AVMs), PAVMs, gastrointestinal AVMs, or hepatic AVMs.[3] Because HHT is underdiagnosed, the etiology of bleeding often remains unknown, nasal and gastrointestinal bleeding predominating. Many patients develop anemia and receive blood transfusions but are unaware that they have AVMs that can be treated.

The diagnosis of HHT is primarily based on the International Clinical Diagnostic (Curaçao) Criteria,[1] which are clinical and radiological criteria for the diagnosis of HHT. HHT accounts for 80-95% of all PAVMs.[1,5] When a diagnosis of HHT cannot be established, PAVMs are classified as idiopathic (iPAVMs). Pulmonary hypertension (PH) is rarely present and can be due to increased pulmonary vascular flow, hepatic AVMs, or anemia.[6] A small proportion of cases are associated with genetic abnormalities.[7,8]

In the past, PAVMs were treated surgically, the rate of complications being high.[9,10] In 1977, Porstmann[11] performed the first catheter embolization using coils, introducing the possibility of percutaneous transcatheter embolization for the treatment of PAVMs. Because percutaneous transcatheter embolization is much less invasive than surgery, it reduces the length of hospital stay and the number of complications. Even in asymptomatic patients, PAVMs should be treated with embolization if they have a feeding artery diameter > 3 mm, in order to prevent infectious complications and strokes.[3,12] Surgery is currently reserved for cases in which percutaneous

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transcatheter embolization fails, feeding artery diameter is too large, or vascular anatomy precludes treatment with embolization.[13] Lung transplantation should be reserved for exceptional cases.[4]

In the present study, we sought to present a case series of PAVM patients followed at a pulmonology outpatient clinic in the city of São Paulo, Brazil, describing the main clinical findings, the number/location of PAVMs, the clinical complications, and the treatment administered.

METHODS

Study population

This was a retrospective observational study, in which electronic medical records were reviewed for all patients referred to the Pulmonary Circulation Outpatient Clinic of the University of São Paulo *Hospital das Clínicas Instituto do Coração* (InCor, Heart Institute) between 2010 and 2017 for AVM evaluation. After clinical evaluation, the Curaçao Criteria[1] were used in order to confirm the diagnosis of HHT: 1) presence of epistaxis; 2) presence of telangiectasias, particularly on the lips, tongue, and fingers; 3) presence of cerebral AVMs, PAVMs, or gastrointestinal AVMs; and 4) a family history of HHT. Patients meeting at least three of the aforementioned criteria were diagnosed with definite HHT.[1,14] The remaining patients were diagnosed with iPAVM. After clinical examination, all patients underwent chest x-ray, chest CT angiography, cranial CT angiography, transthoracic echocardiography, and SpO_2 measurement.

Percutaneous transcatheter embolization was performed with an Amplatzer® device (AGA Medical Corporation, Golden Valley, MN, USA) or coils, depending on their availability. The InCor protocol for percutaneous transcatheter embolization includes the following: local anesthesia; cardiopulmonary monitoring; and systemic unfractionated heparin administered as a bolus of 2,500 IU per hour, approximately. The procedure is performed without antibiotic prophylaxis.

RESULTS

Clinical and demographic data

A total of 41 patients were selected for inclusion in the present study. Of those, 8 were excluded: 7 met three of the Curaçao Criteria for HHT but had no PAVMs, and 1 met only one of the Curaçao Criteria (i.e., a family history of HHT). Of the remaining 33 patients, 27 met the diagnostic criteria for HHT and 6 were classified as having iPAVM. Therefore, two groups were formed: the HHT group, comprising 27 patients, and the iPAVM group, comprising 6 patients (Figure 1).

Demographic data had been collected at the first outpatient visit. In the HHT group, the mean age was 49.6 ± 16.9 years and females predominated (n = 24). Of the 27 patients in the HHT group, 24 (89.0%) had telangiectasias, predominantly on the lips and tongue (Figure 2). None of the patients had digital clubbing. In the initial evaluation, 5 patients (18.5%) had dyspnea. Of those, 4 were functional class II and 1 was functional class III. Of the 5 HHT patients who presented with dyspnea, 4 had an SpO_2 of < 90% (mean, 84.5%; range, 78.0-89.0%) and 1 had an SpO_2 > 90%. Another 2 patients had an SpO_2 of < 90% but no respiratory symptoms. The most common clinical finding in the HHT group was epistaxis (in 100%). None of the patients in the group reported hemoptysis. Cranial CT angiography revealed cerebral AVMs in only 2 (7%) of the patients in the HHT group. None of the patients had a history of gastrointestinal bleeding.

In the iPAVM group, the mean age was 48.1 ± 17.3 years and females predominated (n = 5). Of the 6 patients in the group, 4 had dyspnea. Of those, 2 were functional class II, 1 was functional class III, and 1 was functional class IV. Of the 4 iPAVM patients who presented with dyspnea, 3 had an SpO_2 of < 90% (mean, 83.0%; range, 77.0-89.0%). One patient had an SpO_2 of < 90% but reported no dyspnea, and 2 had an SpO_2 > 90% and no respiratory symptoms (Table 1). None of the patients in the group had recurrent epistaxis.

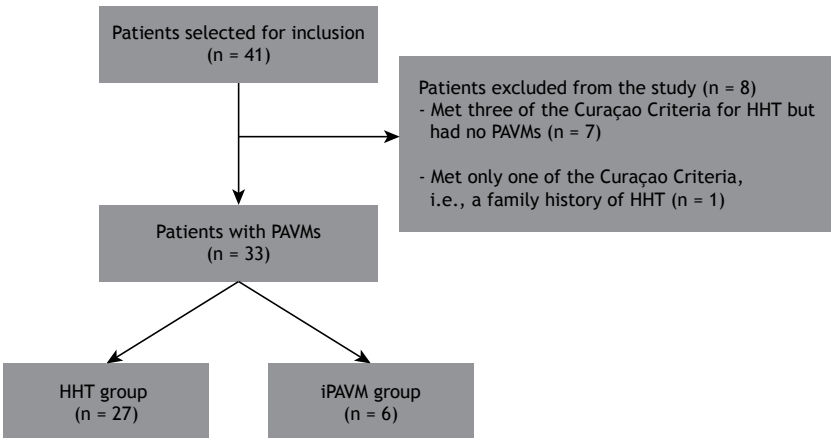

Figure 1. Patients with pulmonary arteriovenous malformations (PAVMs) divided into two groups. HHT: hereditary hemorrhagic telangiectasia; and iPAVM: idiopathic pulmonary arteriovenous malformation.

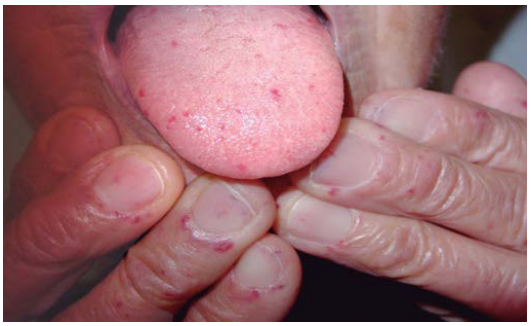

Figure 2. Photograph showing telangiectasias on the lips and fingers of a patient with hereditary hemorrhagic telangiectasia.

Echocardiography, chest CT angiography, and cranial CT angiography

A total of 25 patients (83.3%) underwent echocardiography. One patient (in the HHT group) was suspected of having PH. The patient in question underwent echocardiography twice, pulmonary artery systolic pressure being above the reference value on both examinations (48 mmHg and 53 mmHg). A total of 7 patients underwent microbubble contrast-enhanced echocardiography. In all 7, the microbubble contrast agent passed from the right to the left side of the heart after the third cycle, the presence of intrapulmonary shunt therefore being confirmed. Shortly after being examined, 1 patient experienced visual disturbance and headache lasting approximately 1 h, with good clinical progression. Two patients had cerebral AVMs.

Chest CT angiography showed 101 PAVMs in the HHT group and 7 in the iPAVM group. Of the 101 PAVMs observed in the HHT group, 14 (13.8%) were located in the right upper lobe, 15 (14.8%) were located in the middle lobe, 35 (34.6%) were located in the right lower lobe, 5 (4.9%) were located in the left upper lobe, 11 (10.8%) were located in the lingula, and 22 (21.7%) were located in the left lower lobe (Figure 3A). Of the 7 PAVMs observed in the iPAVM group, 1 (14.2%) was located in the right upper lobe, 3 (42.9%) were located in the right lower lobe, and 3 (42.9%) were located in the left lower lobe. Of the 6 patients in the iPAVM group, 5 had 1 PAVM and 1 had two (Table 1). As can be seen in Figure 3B, the lower lobes were more commonly affected than the upper lobes in the HHT group (56.4% vs. 43.6%) and in the iPAVM group (85.7% vs. 14.2%).

Complications

All patients were evaluated for complications of PAVMs. One patient had cerebral, subphrenic, and psoas abscesses. Hemothorax and pleural empyema were found in 2 patients from the same family, and bacterial endocarditis was found in 1 patient.

Treatment

Embolization

All patients who underwent embolization had PAVMs with a feeding artery diameter of ≤ 20 mm (Figures 4 and 5), Amplatzer® devices and coils being used depending on their availability. Of the 27 patients in the HHT group, 8 (30.7%) required two or more embolization procedures for the treatment of PAVMs, 10 underwent one procedure, and 9 were scheduled to undergo treatment at this writing (1 having undergone one procedure in another country). In the iPAVM group, embolization was successful in 4 patients, their SpO_2 having improved. One patient had a complex PAVM and underwent three embolization procedures. All three were unsuccessful, the patient therefore being referred for pulmonary lobectomy. At this writing, 1 patient was scheduled to undergo treatment. No serious complications occurred during the procedures, and only 2 patients experienced pleuritic chest pain 48 h after the procedure, improving with the use of analgesics.

Post-treatment follow-up

All patients were followed at the Pulmonary Circulation Outpatient Clinic of the InCor and evaluated three months after the procedure, at which time the need for another embolization procedure was assessed. After completing the treatment, patients underwent annual clinical evaluations. At this writing, there were no deaths among the study population.

DISCUSSION

It is known that PAVMs can cause serious complications, such as stroke and brain abscess, as well as massive hemorrhage. To our knowledge, ours is the first study in Latin America to report a large number of PAVM cases of varying etiologies.[15,16] Females predominated in the two study groups. Patients with HHT were more symptomatic than those with iPAVM, as well as having more PAVMs. For all patients, the initial treatment was percutaneous transcatheter embolization with coils or Amplatzer® devices.

Of the 41 patients selected for inclusion, 33 had PAVMs. Of those, 27 (87%) and 6 (13%) were diagnosed with HHT and iPAVM, respectively. This constitutes evidence that HHT is the primary cause of PAVMs, as reported elsewhere.[1,4] HHT is a hereditary vascular disorder whose primary symptom is epistaxis, seen in more than 90% of patients.[13] The fact that 100% of the HHT patients in the present study reported epistaxis is evidence that recurrent epistaxis is an important feature of HHT. In contrast, none of the iPAVM patients in the present study reported epistaxis. Therefore, findings of PAVM and recurrent epistaxis should raise the suspicion of HHT.

With regard to hypoxemia, an SpO_2 of < 90% was found in 15% of the HHT patients and in 66% of the iPAVM patients in the present study. This finding is important when PAVM cases of varying etiologies are compared, because the number of PAVMs at diagnosis and treatment initiation is highest in patients with HHT.[1] One possible explanation for our finding of a much lower proportion of patients with an SpO_2 of <

Table 1. General patient and treatment characteristics.

HHT group	Age, years	Sex	Location of telangiectasias	Other AVMs	Dyspnea	Epistaxis	Brain abscess	SpO2	PAVMs (n)	PAVM location	Number of embolization procedures
1	38	F	Lips	-	FC I	+	-	100%	1	1 RLL	2
2	56	M	Lips	-	FC II	+	-	98%	3	2 RLL / 1 LLL	2
3	50	M	Lips	-	FC I	+	+	94%	5	1 RUL / 1 ML / 2 RLL /1 LLL	2
4	50	F	Tongue/Lips	-	FC I	+	-	96%	4	2 RLL/ 1 Lingula / 1 LLL	2
5	19	F	-	-	FC II	+	-	86%	6	3 ML / 2 RLL / 1 LLL	scheduled*
6	46	F	Tongue	-	FC I	+	-	96%	6	1 ML / 3 RLL / 2 LLL	1
7	69	F	-	-	FC I	+	-	98%	3	2 RLL / 1 Lingula	2
8	36	F	Tongue/Fingers	-	FC I	+	-	98%	1	1 ML	scheduled*
9	72	F	Tongue/Fingers	-	FC I	+	-	96%	2	1 RLL / 1 LLL	scheduled*
10	46	F	Lips/Tongue	-	FC I	+	-	99%	3	3 RLL	1
11	21	M	Tongue	Hepatic	FC I	+	-	96%	6	3 Lingula / 2 RLL / 1 LLL	1
12	73	M	Lips	-	FC I	+	-	96%	2	1 RUL / 1 LLL	1
13	50	F	Tongue	-	FC II	+	-	78%	12	3 RUL / 3 RLL / 2 LUL / 4 LLL	1
14	71	F	Lips	-	FC I	+	-	85%	4	1 RUL / 1 RLL / 1 LUL / 1 Lingula	scheduled*
15	68	F	Lips/Tongue/Fingers	-	FC I	+	-	98%	4	1 RUL / 2 RLL / 1 LLL	2
16	31	F	Lips	-	FC I	+	-	84%	7	2 RUL / 1 ML / 1 RLL/ 2 Lingula / 1 LLL	scheduled*
17	18	F	Tongue	-	FC I	+	-	93%	5	1 ML / 2 RLL / 1 Lingula/ 1 LLL	1
18	71	F	Lips/Tongue/Fingers	-	FC I	+	-	95%	6	2 RUL / 1 ML / 1 RLL/ 2 LLL	1
19	69	F	Tongue/Fingers	-	FC II	+	-	94%	3	1 ML / 1 RLL / 1 Lingula	2
20	64	F	Lips/Tongue/Fingers	-	FC I	+	-	98%	3	1 RUL / 1 LUL / 1 LLL	scheduled*
21	45	F	Lips	-	FC I	+	-	95%	6	2 RUL / 2 ML / 1 RLL / 1 LLL	3
22	52	F	Lips/Tongue	-	FC I	+	-	99%	1	1 RLL	1
23	55	F	Tongue/Mouth/Fingers	-	FC I	+	-	98%	1	1 LLL	scheduled*
24	57	M	Tongue/Lips/Fingers	Cerebral	FC III	+	-	85%	2	1 RLL / 1 LLL	1
25	30	F	Tongue/Lips	-	FC I	+	-	97%	1	1 RLL	scheduled*
26	34	M	-	Cerebral	FC I	+	-	93%	3	1 ML / 1 RLL / 1 LLL	scheduled*
27	48	F	Tongue	-	FC II	+	-	89%	1	1 RLL	1
iPAVM group											
1	70	F	-	-	FC IV	-	-	89%	1	1 RUL	1
2	32	M	-	-	FC II	-	-	86%	1	1 RLL	1
3	57	F	-	-	FC III	-	-	82%	2	2 LLL	scheduled*
4	23	F	-	-	FC I	-	-	77%	1	1 LLL	3
5	52	F	-	-	FC I	-	-	95%	1	1 RLL	1
6	55	F	-	-	FC II	-	-	91%	1	1 RLL	1

HHT: hereditary hemorrhagic telangiectasia; iPAVM: idiopathic pulmonary arteriovenous malformation; PAVM: pulmonary arteriovenous malformation; AVM: arteriovenous malformation; FC: functional class; RUL: right upper lobe; ML: middle lobe; RLL: right lower lobe; LUL: left upper lobe; and LLL: left lower lobe. *Patients who at this writing were scheduled to undergo transcatheter embolization.

90% in the HHT group is that, although patients with HHT present with more PAVMs than do those with iPAVM, pulmonary shunt is more severe in the latter.

In the present study, PAVMs were predominantly located in the lower lobes, a finding that is consistent with those of another study.[1] This finding suggests that there was no significant relationship between PAVM location and the fact that the proportion of patients with hypoxemia was higher in the iPAVM group than in the HHT group. It is of note that the patients who had reduced SpO_2 levels were mildly symptomatic and had dyspnea on exertion only; this might be due to an adaptive response to hypoxemia (i.e., acclimatization).[17,18]

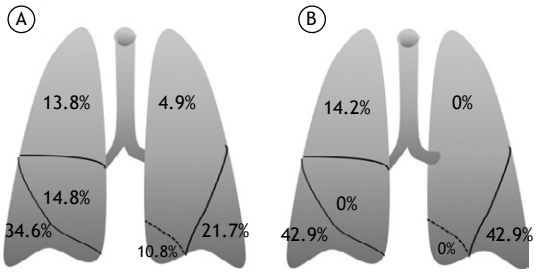

Figure 3. In A, location of pulmonary arteriovenous malformations in the group of patients with hereditary hemorrhagic telangiectasia (n = 101). In B, location of pulmonary arteriovenous malformations in the group of patients with idiopathic pulmonary arteriovenous malformations (n = 7).

It has been reported that 10-20% of patients with HHT have cerebral AVMs.[13] Patients with HHT should be screened for cerebral AVMs because of the risk of serious complications such as bleeding, with an estimated risk of 0.5% per year.[3] In the present study, cerebral AVMs were found in 2 patients (7%). This is probably due to the fact that magnetic resonance imaging of the brain and cerebral arteriography were not performed, cranial CT angiography being the only examination performed.

Of the 27 patients with HHT in the present study, 2 (7.4%) had infectious complications: brain abscess, in 1, and bacterial endocarditis (occurring within 1 year after percutaneous transcatheter embolization), in 1. The aforementioned patient and another from the same family had pleural empyema. In order to prevent infections, patients with PAVMs should receive antibiotic prophylaxis for dental procedures.[13] It is extremely important to screen HHT patients for infectious complications, which in some cases are the first manifestations of HHT, appearing before the diagnosis of PAVM is made.[6]

Another finding in patients with HHT is PH, which can be due to hepatic AVMs,[19] anemia, increased

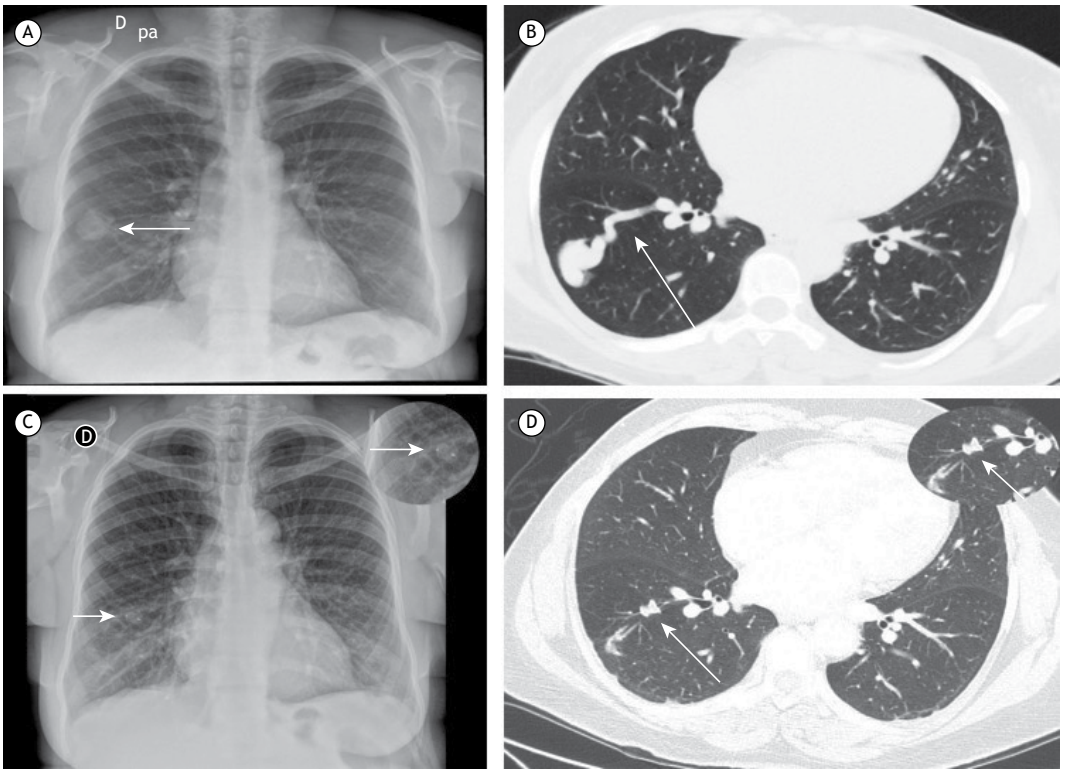

Figure 4. In A, chest X-ray taken before embolization and showing a nodule in the lower third of the right hemithorax (arrow). In B, chest CT angiography performed before embolization and showing an arteriovenous malformation in the right lower lobe (arrow). In C, chest X-ray taken after embolization and showing an Amplatzer® device in the lower third of the right hemithorax (arrow; see also the enlarged inset). In D, chest CT angiography performed after embolization and showing a reduction in pulmonary arteriovenous malformation sac size, as well as the Amplatzer® device in the right lower lobe (arrow; see also the enlarged inset).

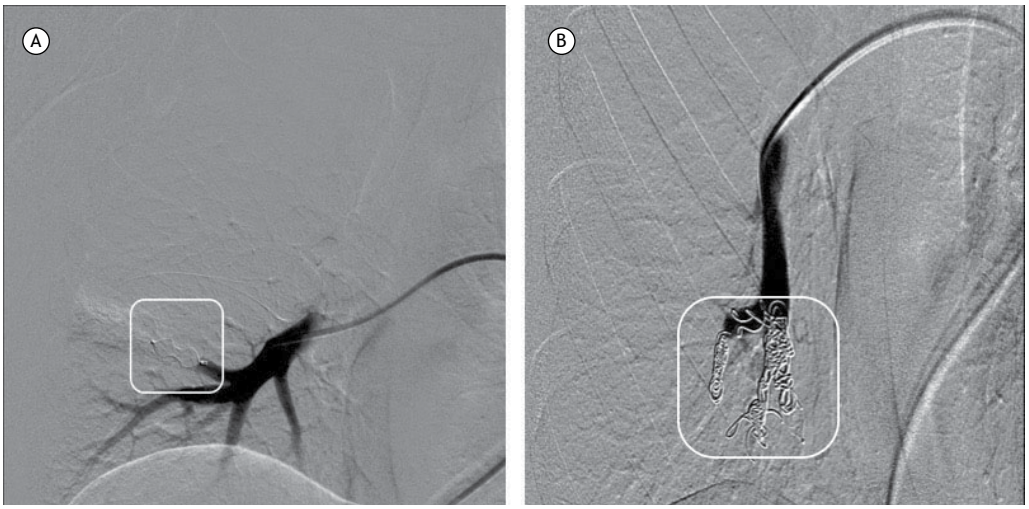

Figure 5. Arteriography performed after embolization. In A, Amplatzer® device; in B, coils.

pulmonary vascular flow, or genetic abnormalities, the last of the four affecting the *ENG* gene on chromosome 9 or the *ACVRL1* gene on chromosome 12.[20] In the present study, PH was suspected in 1 patient (3.7%), who underwent echocardiography twice and had no anemia. No right heart catheterization was performed to confirm the diagnosis of PH.

Transcatheter embolization is the best treatment option for patients with PAVMs, including asymptomatic patients.[21] It is an important treatment option because it improves hypoxemia and prevents ischemic stroke and infectious complications caused by right-to-left shunt.[22-24] Percutaneous transcatheter embolization is currently the most widely used treatment for AVMs in patients with HHT and in those with iPAVMs.[1] Multiple PAVMs can be treated during a single procedure; however, in patients with many PAVMs and in those with several complex PAVMs, it is best to perform several embolization procedures on different days.[13] In the present study, 30.7% of the patients underwent two or more embolization procedures on separate occasions, at least three weeks apart. Complications included pleuritic chest pain 48 h after the procedure in 2 patients (6.25%), who improved with pharmacological treatment. Pleuritic chest pain is considered a benign complication, occurring in 10% of cases; it is a transient complication, being associated with diffuse or peripheral PAVMs.[25] Major complications include pulmonary infarction, device migration, gas embolism, transient angina, cardiac arrhythmia, and pneumothorax, which have been reported to occur in approximately 1% of cases when treatment is performed at experienced centers.[13] Contraindications to percutaneous embolization include pregnancy, PH, and kidney failure.[26] However, in some cases, the benefits outweigh the risks, and the decision to perform the procedure should be made on a case-by-case basis.[27] At this writing, 1 patient with PH was under evaluation for possible embolization, an interventional radiology team being involved in the decision-making process.

A follow-up evaluation should be carried out 3-6 months after the embolization procedure, consisting of clinical examination and imaging (e.g., a chest X-ray).[6] Although SpO_2 increases shortly after the procedure, a reduction in PAVM sac size and complete resolution of the PAVM occur within 6 months.[23,28,29] There is no consensus regarding when CT angiography should be performed again.[6]

Surgical resection is reserved for complex cases[13] or cases in which embolization is unsuccessful. Of the 33 PAVM patients in the present study, only 1 was referred for surgical resection (after three failed embolization procedures).

The limitations of the present study include its retrospective design at a single institution (a pulmonary circulation outpatient clinic) and the fact that the number of patients in each group was markedly different, precluding a straightforward between-group comparison. Despite variations in the diagnosis, treatment, and follow-up of PAVMs, the best option for patients with PAVMs is to be followed by a multidisciplinary team at a specialized center.[17,27,30,31]

In summary, females predominated in our study, as did PAVMs located in the lower lobes. Few clinical complications were encountered. The majority of patients with HHT had multiple PAVMs and epistaxis, as well as having no respiratory symptoms or hypoxemia. The majority of patients with iPAVMs had only one PAVM, as well as having dyspnea and hypoxemia. In all cases, the initial treatment was percutaneous transcatheter embolization.

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Translation and cultural adaptation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer Module for quality of life assessment in patients with lung cancer in Brazil

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ABSTRACT

Objective: To translate the European Organisation for Research and Treatment of Cancer (EORTC) 29-item Quality of Life Questionnaire-Lung Cancer Module (QLQ-LC29, developed for the assessment of quality of life in patients with lung cancer) to Portuguese, conducting a pilot study of the Portuguese-language version and adapting it for use in Brazil. **Methods:** For the translation, cultural adaptation, and pilot testing of the QLQ-LC29, we followed the guidelines established by the EORTC. The translation (English → Portuguese) and back-translation (Portuguese → English) were both carried out by translators, working independently, who were native speakers of one language and fluent in the other. After review, a draft version was created for pilot testing in lung cancer patients in Brazil. **Results:** A total of 15 patients diagnosed with lung cancer completed the Portuguese-language version of the questionnaire. At the end of the process, we conducted a structured interview to identify any patient difficulty in understanding any of the questions. The final versions were sent to the EORTC and were approved. **Conclusions:** The Portuguese-language version of the EORTC QLQ-LC29 appears to be a useful, important, reliable questionnaire that is a valid tool for assessing quality of life in patients with lung cancer in Brazil.

Keywords: Surveys and Questionnaires; Lung neoplasms; Quality of Life; Brazil; Translations.

INTRODUCTION

Over the past 100 years, lung cancer has changed from a rare disease to a real global problem. Scientific and clinical efforts to improve outcomes have led to a better understanding not only of the etiology of lung cancer but also of the histological and molecular characteristics of individual lung tumors.[1]

Lung cancer is the most commonly diagnosed cancer (11.6% of all cancer cases) and the leading cause of cancer death (18.4% of all cancer deaths) worldwide; its prevalence is increasing among women and has surpassed that of breast cancer in 28 countries.[2] In Brazil, lung cancer is considered the most deadly type of cancer among men and women. A total of 18,740 and 12,530 new cases of lung cancer are estimated among men and women, respectively, for each year of the 2018-2019 biennium. This corresponds to an estimated risk of 18.16 new cases per 100,000 men and an estimated risk of 11.81 new cases per 100,000 women, lung cancer being the second most common type of cancer in Brazil.[3]

Although lung cancer is predominantly caused by tobacco smoke, approximately 25% of all lung cancers worldwide are not attributable to this etiology.[4] Other etiologies include environmental exposure to smoke, radiation, or smoke from burning wood; occupational exposures; oncogenic viruses; genetic alterations; and changes in sex hormone levels.[4,5]

The concept of quality of life (QoL) is broad, subjective, and encompasses four main domains: physical well-being; psychological well-being; social well-being; and occupational well-being.[6,7] In cancer patients, QoL care and attention to QoL are even greater, because QoL can not only be a predictor of morbidity and mortality but can also serve as a parameter for evaluating treatment course and response.[7]

Several generic QoL scales are used in Brazil and worldwide; however, it is important that the instrument chosen for use be as specific as possible so that it can provide information as accurately as possible. With this in mind, the European Organisation for Research and

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Treatment of Cancer (EORTC) developed a variety of instruments to assess QoL in patients with cancer.[8] The core questionnaire is the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), which includes five functional scales, three symptom scales, and a global health and QoL scale.[9] However, the use of the EORTC QLQ-C30 prompted the need for instruments that could assess the specificity and particularities of each type of cancer more specifically, which resulted in a multitude of modules for different types of cancer.[10] One of these modules is known as the 29-item QLQ-Lung Cancer Module (QLQ-LC29), the objective of which is to assess QoL in patients with lung cancer.[11,12] The EORTC QLQ-LC29 was developed as an update to the previous lung cancer module, the EORTC QLQ-LC13, because of important advances in lung cancer treatment and in QoL assessment.[11]

The objective of the present study was to translate the original English-language version of the EORTC QLQ-LC29 to Portuguese, adapting it for use in Brazil, in order to provide an appropriate tool for assessing QoL in patients with lung cancer in the country.

METHODS

This was a methodological study whose objective was to translate and culturally adapt the QLQ-LC29, which is a module for specifically assessing QoL in patients with lung cancer. The final version has 29 items and refers to a specific time period (i.e., "during the past week"). Patients also have the opportunity to report whether there were symptoms or problems that were not covered by the questionnaire, but were relevant for them during the past week. Each item is scored on a 4-point scale (Not at All; A Little; Quite a Bit; and Very Much).

Translation procedure

The translation was made along with the cultural adaptation and the pilot testing authorized by the EORTC Quality of Life Department and carried out in accordance with the EORTC translation procedure.[13]

The original English-language version was translated by two translators, working independently, who were native speakers of Portuguese and fluent in English. Subsequently, a reconciled translation was made on the basis of the two translations, that is, a third person analyzed the two translations to achieve the best possible version by choosing one of the two translations or by combining them on the basis of their similarities, wording, etc. The next step was to translate the reconciled version back into English, which was done by two translators who were native speakers of or fluent in English. The result of these steps (forward translation, reconciliation, and backward translation with comments) was put into a translation report that was reviewed by the EORTC translation unit. In the review of the report, all suggestions and corrections were analyzed and discussed. Once the discussion reached a consensus, the translation could undergo linguistic validation (pilot testing).

Pilot testing

Pilot testing, in accordance with the EORTC translation procedure,[13] includes a group of 10 to 15 patients, who are invited to complete the questionnaire. After completion of the questionnaire, a structured interview focusing on each item, one by one, is conducted to investigate whether participants would report any difficulty answering the questions and whether they found any item to be confusing, upsetting, or offensive, or to contain difficult vocabulary. All of the participants' comments should be pooled and summarized in a pilot-testing report, which should be sent for review to the EORTC translation unit. Once all comments have been analyzed and discussed, the EORTC translation unit prepares the final version of the translation and closes the project.

Participants

This was a convenience sample in which patients were randomly recruited from the Oncology Department of the Santa Terezinha University Hospital, located in the city of Joaçaba, Brazil. Patient status was determined from the medical records, and only patients with a diagnosis of lung cancer were considered study participants.

Inability to understand or complete the questionnaire was considered an exclusion criterion. There were no restrictions regarding gender, age, or level of education. All participating patients were receiving cancer treatment and were approached at the time of their medical visit. It should be highlighted that the EORTC procedures for questionnaire translation do not stipulate a single time point during the course of the disease for patient assessment, this time point (diagnosis, treatment, or control) being random. The study was approved by the Human Research Ethics Committee of the *Universidade do Oeste de Santa Catarina* and the Santa Terezinha University Hospital (Protocol no. 2.286.701 of September 20, 2017).

Statistical analysis

Once the interviews were completed, all data were compiled and analyzed using simple descriptive statistics. Understandability was assessed using a Likert scale preceded by the question, "Did you understand what was asked?"—0: I did not understand anything; 1: I understood only a little; 2: I somewhat understood it; 3: I understood almost everything, but I have some questions; 4: I understood almost everything; and 5: I understood it perfectly well, and I have no questions.[14] The internal consistency of the scale was calculated with Cronbach's alpha coefficient. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Fifteen patients participated in the present study, 8 of whom were female. The mean age was 61 ± 5.2 years. Thirteen patients (86.7%) had attended only elementary school, and 2 patients (13.3%) had completed high school.

Table 1. Original English-language version, translations, back-translations, and final Brazilian Portuguese-language version of the Quality of Life Questionnaire-Lung Cancer 29.

#	Original English-language version	Translation	Selected translation	Back-translation	Final Brazilian Portuguese-language version
1	Have you coughed?	(T1) Você tem tido tosse? (T2) Você tem tossido?	T2	(R1) Have you coughed? (R2) Have you coughed up?	Você teve tosse?
2	Have you coughed up blood?	(T1) Tossiu sangue? (T2) Você tem tossido sangue?	T2	(R1) Have you coughed up blood? (R2) Have you coughed up blood?	Você teve tosse com sangue?
3	Have you been short of breath when you rested?	(T1) Sentiu falta de ar enquanto repousava? (T2) Você sentiu falta de ar quando descansava?	T2	(R1) Have you been breathless when you rested? (R2) Have you been short of breath when you rested?	Você teve falta de ar quando descansava?
4	Have you been short of breath when you walked?	(T1) Sentiu falta de ar enquanto andava? (T2) Você sentiu falta de ar quando caminhava?	T2	(R1) Have you been breathless when you walked? (R2) Have you been short of breath when you rested?	Você teve falta de ar quando caminhava?
5	Have you been short of breath when you climbed stairs?	(T1) Sentiu falta de ar enquanto subia escadas (se subisse)? (T2) Você sentiu falta de ar enquanto subia escadas quando subiu escadas? (se subiu)	T2	(R1) Have you been breathless when you climbed stairs? (R2) Have you been short of breath when you climbed stairs?	Você teve falta de ar quando subiu escadas?
6	Have you had a sore mouth or tongue?	(T1) Sentiu sua boca ou língua doloridas? (T2) Você sentiu dor na boca ou língua?	T2	(R1) Have you had a sore mouth or tongue? (R2) Have you had a sore mouth or tongue?	Você teve sua boca ou língua doloridas?
7	Have you had problems swallowing?	(T1) Sentiu dificuldade ao engolir? (T2) Você sentiu dificuldade para engolir?	T2	(R1) Have you had problems swallowing? (R2) Have you had problems swallowing?	Você teve problemas para engolir?
8	Have you had tingling hands or feet?	(T1) Você teve sensação de formigamento nas mãos ou pés? (T2) Teve dormência (formigamento) nas mãos ou pés?	T1	(R1) Have you had tingling hands or feet? (R2) Have you had numbness on hands or feet?	Você teve sensação de formigamento nas mãos ou pés?
9	Have you had hair loss?	(T1) Você tem queda de cabelo? (T2)Você já perdeu cabelo?	T1	(R1) Have you had hair loss? (R2) Have you had hair loss?	Você teve queda de cabelo?
10	Have you had pain in your chest?	(T1) Você tem sentido dores no peito? (T2) Você já sentiu dores no peito?	T1	(R1) Have you had pain in your chest? (R2) Have you had pain in your chest?	Você teve dores no peito?
11	Have you had pain in your arm or shoulder?	(T1) Você sentiu dores no braço ou ombro? (T2) Você sentiu dores no braço ou ombro?	T1=T2	(R1) Have you had pain in your arm or shoulder? (R2) Have you had pain in your arm or shoulder?	Você teve dores no braço ou ombro?
12	Have you had pain in other parts of your body?	(T1) Sentiu dores em outras partes de seu corpo? (T2) Você já sentiu dores em outras partes do seu corpo?	T2	(R1) Have you had pain in other parts of your body? (R2) Have you had pain in other parts of your body?	Você teve dores em outras partes do seu corpo?
13	Have you had allergic reactions?	(T1) Você já teve reações alérgicas? (T2) Você já teve reações alérgicas?	T1=T2	(R1) Have you had allergic reactions? (R2) Have you had allergic reactions?	Você teve reações alérgicas?
14	Have you had burning or sore eyes?	(T1) Teve ardência ou irritação nos olhos? (T2) Você já sentiu ardência ou irritação nos olhos?	T2	(R1) Have you had burning or sore eyes? (R2) Have you had burning eyes?	Você teve ardência ou irritação nos olhos?

Table 1. Continued...

#	Original English-language version	Translation	Selected translation	Back-translation	Final Brazilian Portuguese-language version
15	Have you been dizzy?	(T1) Você ficou tonto? (T2) Você já se sentiu tonto?	T2	(R1) Have you been dizzy? (R2) Have you felt dizzy?	Você teve tonturas?
16	Have you had splitting fingernails or toenails?	(T1) Você já teve rachaduras nas unhas das mãos ou pés? (T2) Você já teve as unhas das mãos ou pés quebradas?	T2	(R1) Have you had splitting fingernails or toenails? (R2) Have you had cracking fingernails or toenails?	Você teve as unhas das mãos ou pés quebradas?
17	Have you had skin problems (e.g. itchy, dry)?	(T1) Você teve problemas de pele (ex.: coceira, pele seca)? (T2) Você já teve problemas na pele (ex: coceira, pele seca)?	T2	(R1) Have you had skin problems (e.g. itchy, dry)? (R2) Have you had skin problems (e.g. itchy, dry)?	Você teve problemas na pele (ex.: coceira, pele seca)?
18	Have you had problems speaking?	(T1) Sentiu dificuldades para falar? (T2) Você já sentiu dificuldades para falar?	T2	(R1) Have you had problems speaking? (R2) Have you had problems speaking?	Você teve problemas para falar?
19	Have you been afraid of tumor progression?	(T1) Tem medo da progressão tumoral? (T2) Você tem medo da progressão do tumor?	T2	(R1) Have you been afraid of tumor progression? (R2) Have you been afraid of tumor progression?	Você teve medo da progressão do tumor?
20	Have you had thin or lifeless hair as a result of your disease or treatment?	(T1) Você teve um afinamento do cabelo ou o mesmo ficou sem vida como resultado do tratamento ou da sua doença? (T2) Você teve um cabelo mais fino ou sem vida como resultado da doença ou do tratamento?	T1	(R1) Have you had thin or lifeless hair as a result of your disease or treatment? (R2) Have you had thin or lifeless hair as a result of your illness or treatment?	Você teve um afinamento do cabelo ou o mesmo ficou sem vida como resultado de sua doença ou tratamento?
21	Have you worried about your health in the future?	(T1) Você já se preocupa com sua saúde no futuro? (T2) Você tem se preocupado com sua saúde no futuro?	T2	(R1) Have you worried about your health in the future? (R2) Have you worried about your health in the future?	Você teve preocupações com sua saúde no futuro?
22	Have you had dry cough?	(T1) Você teve tosse seca? (T2) Você já teve tosse seca?	T2	(R1) Have you had dry cough? (R2) Have you had dry cough?	Você teve tosse seca?
23	Have you experienced a decrease in your physical capabilities?	(T1) Você sofreu uma diminuição nas suas capacidades físicas? (T2) Você sentiu que sua capacidade física tem diminuído?	T2	(R1) Have you noticed a decrease in your physical capabilities? (R2) Have you noticed a decrease in your physical capacities?	Você teve a sensação de que sua capacidade física diminuiu?
24	Has weight loss been a problem for you?	(T1) A perda de peso foi um problema para você? (T2) A perda de peso tem sido um problema para você?	T2	(R1) Has weight loss been a problem for you? (R2) Has weight loss been a problem for you?	A perda de peso foi um problema para você?
25	Have you had pain in the area of surgery?	(T1) Você sofreu dor na área de cirurgia? (T2) Você já sentiu dores na área da cirurgia?	T2	(R1) Have you had pain in the area of surgery? (R2) Have you had pain in the area of surgery?	Você teve dores na área da cirurgia?
26	Has the area of your wound been oversensitive?	(T1) A área da sua lesão foi muito sensível? (T2) A área da sua ferida ficou muito sensível?	T2	(R1) Has the area of your wound been oversensitive? (R2) Has the area of your lesion been highly sensitive?	A área da sua ferida ficou muito sensível?
27	Have you been restricted in your performance due to the extent of surgery?	(T1) Você foi restringido em seu desempenho devido à extensão da cirurgia? (T2) Você teve seu desempenho limitado pela extensão da cirurgia?	T2	(R1) Have you been restricted in your performance due to the extent of surgery? (R2) Have you had your performance limited due to the extent of surgery?	Você teve restrição do seu desempenho devido à extensão da cirurgia?

Table 1. Continued...

#	Original English-language version	Translation	Selected translation	Back-translation	Final Brazilian Portuguese-language version
28	Have you had any difficulty using your arm or shoulder on the side of the chest operation?	(T1) Você teve alguma dificuldade em usar seu braço ou ombro no lado da operação do peito? (T2) Você teve alguma dificuldade de movimentar o braço ou ombro no lado da cirurgia?	T2	(R1) Have you had any difficulty using your arm or shoulder on the side of the chest operation? (R2) Have you had any difficulty moving your arm or shoulder on the side of the chest operation?	Você teve alguma dificuldade de usar o braço ou ombro no lado da cirurgia?
29	Has your scar pain interfered with your daily activities?	(T1) Sua dor de cicatriz interferiu com suas atividades diárias? (T2) A dor da sua cicatriz tem interferido em suas atividades diárias?	T2	(R1) Has your scar pain interfered with your daily activities? (R2) Has your scar pain interfered with your daily activities?	A dor da sua cicatriz interferiu em suas atividades diárias?
	Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the past week?	(T1) Ocorreram quaisquer sintomas ou problemas que não foram abordados pelo questionário, mas foram relevantes para você na semana passada? (T2) Aconteceram qualquer outro sintoma ou problema que não foram abordados neste questionário, mas que foram importantes para você, na semana passada?	T1	(R1) Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the past week? (R2) Were there any symptoms or problems that were not covered by the questionnaire, but were relevant for you in the last week?	Ocorreram quaisquer sintomas ou problemas que não foram abordados pelo questionário, mas foram relevantes para você na última semana?

All patients completed the questionnaire in less than 25 minutes, in a designated area within the hospital. Once pilot testing was completed, the comments from patients were analyzed. No difficulties in answering the questions were reported, and none of the items were found to be confusing, upsetting, or offensive, or to contain difficult vocabulary. Therefore, no changes were made to the final version approved by the EORTC translation unit. The Portuguese-language version of the QLQ-LC29 was approved. The steps are described in Table 1.

The understandability of the instrument was good, with a mean of 5.0 points (maximum value of 5.0), and most questions were fully understood (Table 2). The internal consistency of the scale was calculated with Cronbach's alpha coefficient, and an alpha value of 0.94 was found.

The full version of the instrument cannot be published in the present study for copyright reasons. The final version of the instrument can be purchased by consulting the EORTC.

DISCUSSION

This study presents data regarding the translation of the EORTC QLQ-LC29 to Portuguese in Brazil and regarding the cultural adaptation and pilot testing of this Portuguese-language version. This is the first such version, and was authorized and audited by the EORTC, which oversaw all the steps in creating this Portuguese-language version.

The importance of making the EORTC QLQ-LC29 available to scientists and clinicians in the field of oncology is immeasurable, since lung cancer is the most common cancer and is the one with the highest mortality rates and the lowest 5-year survival rates,[3-5] and therefore it is important that patient QoL be a variable taken into account.[6,8] Through the use of a disease-specific tool such as the EORTC QLQ-LC29, it is possible not only to predict patient prognosis or patient morbidity and mortality, but also to inform decisions regarding treatment, especially because the questionnaire provides information about patient clinical status in various domains.[6,11,12,15]

The measurement properties of the original English-language version of the EORTC QLQ-LC29 were evaluated and verified at the time of its creation in a multicenter study.[11] Because the EORTC QLQ-LC29 is a recent module, this is its first translated version, and therefore data are lacking for a comparison between our results and those of other studies. It is expected that, as soon as the original English-language version of the EORTC QLQ-LC29 is widely disseminated, various researchers from different countries and speaking different languages will translate and adapt this module in order to make this disease-specific tool available for assessing QoL in patients with lung cancer.[11]

For each new translation, a series of cultural changes and adaptations are made in order to develop a version specific to a given population and its characteristics.[16,17] This specificity justifies the need for translations and cultural adaptations, considering that a given topic can elicit different answers and different effects because of cultural differences.[10]

Table 2. Assessment of the understandability of the Brazilian Portuguese-language version of the Quality of Life Questionnaire-Lung Cancer 29.

Question	Understandability, mean (SD)	Question	Understandability, mean (SD)
1	5.0 (0.0)	16	5.0 (0.0)
2	5.0 (0.0)	17	5.0 (0.0)
3	5.0 (0.0)	18	5.0 (0.0)
4	5.0 (0.0)	19	5.0 (0.0)
5	5.0 (0.0)	20	5.0 (0.0)
6	5.0 (0.0)	21	4.8 (0.4)
7	5.0 (0.0)	22	5.0 (0.0)
8	5.0 (0.0)	23	4.9 (0.4)
9	5.0 (0.0)	24	5.0 (0.0)
10	5.0 (0.0)	25	5.0 (0.0)
11	5.0 (0.0)	26	5.0 (0.0)
12	5.0 (0.0)	27	4.5 (0.5)
13	4.7 (0.5)	28	5.0 (0.0)
14	5.0 (0.0)	29	5.0 (0.0)
15	5.0 (0.0)		

We acknowledge that our study may have some limitations, such as the size of the pilot-testing sample, which was intentionally selected; however, sampling was carried out in accordance with the EORTC recommendations.[13,18] Despite being small, the sample was sufficient to validate the translated version according to the EORTC recommendations. Data collection with a larger sample would make it possible to perform more complex analyses, including analysis of measurement properties, in accordance with parameters used internationally.[18]

After completion of all the steps described in the present study and analysis of the results, our data suggest that the present Portuguese-language version of the EORTC QLQ-LC29 is suitable for use by scientists and clinicians in Brazil.

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Thoracic calcifications on magnetic resonance imaging: correlations with computed tomography

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ABSTRACT

Objective: To identify the characteristics of thoracic calcifications on magnetic resonance (MR) imaging, as well as correlations between MR imaging and CT findings. **Methods:** This was a retrospective study including data on 62 patients undergoing CT scans and MR imaging of the chest at any of seven hospitals in the Brazilian states of Rio Grande do Sul, São Paulo, and Rio de Janeiro between March of 2014 and June of 2016 and presenting with calcifications on CT scans. T1- and T2-weighted MR images (T1- and T2-WIs) were semiquantitatively analyzed, and the lesion-to-muscle signal intensity ratio (LMSIR) was estimated. Differences between neoplastic and non-neoplastic lesions were analyzed. **Results:** Eighty-four calcified lesions were analyzed. Mean lesion density on CT was 367 ± 435 HU. Median LMSIRs on T1- and T2-WIs were 0.4 (interquartile range [IQR], 0.1-0.7) and 0.2 (IQR, 0.0-0.7), respectively. Most of the lesions were hypointense on T1- and T2-WIs (n = 52 [61.9%] and n = 39 [46.4%], respectively). In addition, 19 (22.6%) were undetectable on T1-WIs (LMSIR = 0) and 36 (42.9%) were undetectable on T2-WIs (LMSIR = 0). Finally, 15.5% were hyperintense on T1-WIs and 9.5% were hyperintense on T2-WIs. Median LMSIR was significantly higher for neoplastic lesions than for non-neoplastic lesions. There was a very weak and statistically insignificant negative correlation between lesion density on CT and the following variables: signal intensity on T1-WIs, LMSIR on T1-WIs, and signal intensity on T2-WIs ($r = -0.13$, $p = 0.24$; $r = -0.18$, $p = 0.10$; and $r = -0.16$, $p = 0.16$, respectively). Lesion density on CT was weakly but significantly correlated with LMSIR on T2-WIs ($r = -0.29$, $p < 0.05$). **Conclusions:** Thoracic calcifications have variable signal intensity on T1- and T2-weighted MR images, sometimes appearing hyperintense. Lesion density on CT appears to correlate negatively with lesion signal intensity on MR images.

Keywords: Calcification, physiologic; Thorax/diagnostic imaging; Tomography, X-ray computed; Magnetic resonance imaging.

INTRODUCTION

Thoracic calcifications are associated with various diseases, including calcified granulomas, metabolic disorders, occupational diseases, and lung metastases, as well as benign and malignant tumors.[1-5] CT is the gold standard method for detecting and characterizing calcifications.[1] There have been few studies of thoracic calcifications on magnetic resonance (MR) imaging, most reports of calcifications on MR imaging being related to intracranial lesions.[6-10]

Calcifications generate nonspecific signal intensities on conventional T1- and T2-weighted images (WIs) and gradient-echo images.[7,8,11] Because calcium salts do not contain mobile protons, they have no signal on MR images, and densely calcified lesions have been classically described as having low signal intensity on T1- and T2-WIs.[6-8,11] However, studies have reported hyperintense, hypointense, and isointense signals on both T1- and T2-WIs, signal intensity depending on the specific composition of aggregates of calcium salts and on particle size.[7,8,11,12]

Although X-rays and CT scans have been extensively used for thoracic evaluation, MR imaging of the chest is an emerging modality.[13-17] It combines functional and

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morphological imaging and is therefore an alternative for patients in whom exposure to ionizing radiation is a concern, including children, pregnant women, and patients undergoing repeat examinations over a long period of time.[13,14] The primary objective of the present study was to identify the characteristics of thoracic calcifications on MR imaging, as well as correlations between MR imaging and CT findings. A secondary objective was to compare calcifications associated with cancer and those not associated with cancer in terms of their MR imaging features.

METHODS

Study participants

This was a retrospective study including data on all patients undergoing CT scans and MR imaging of the chest at any of seven hospitals in the Brazilian states of Rio Grande do Sul, São Paulo, and Rio de Janeiro between March of 2014 and June of 2016. The study was approved by the local research ethics committee (Protocol no. 22758413.8.0000.5335), and the requirement for informed consent was waived.

The inclusion criteria were as follows: thoracic calcifications larger than 0.3 cm on CT scans of the chest and diagnostic-quality chest MR imaging. All of the patients in our study sample had participated in previous studies comparing CT and MR imaging in the assessment of lung nodules and pulmonary vessels, as well as for lung cancer staging. MR imaging and CT scans of the chest were performed in the same week. All patient medical records were reviewed, and lung lesions were classified as neoplastic or non-neoplastic.

MR imaging and CT protocols

All CT examinations were performed with a 64-row multidetector CT scanner (LightSpeed VCT; GE Healthcare, Chicago, IL, USA), the following parameters being used: 120 kVp; 250 mA; rotation time, 0.8 s; and pitch, 1.375. Volumetric inspiratory CT scans were acquired with 1-mm collimation at 1-mm increments and a soft reconstruction algorithm. All CT scans were obtained with mediastinal window settings (width, 350-450 HU; level, 20-40 HU) and lung parenchymal window settings (width, 1,200-1,600 HU; level, −500 HU to −700 HU), reconstructions being performed in the axial and coronal planes.

MR imaging was performed with a 1.5-T scanner (Magnetom Aera; Siemens Healthineers, Erlangen, Germany). A dedicated 12-element integrated matrix coil system covering the entire thorax was used for signal reception.[18] The system consists of two flexible phased-array coils (one anterior coil and one posterior coil), each containing a set of six receiver elements.[18] A half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence was used, and the field of view was adapted to each patient. The HASTE sequence was performed with respiratory gating based on diaphragm navigator. Sequence parameters were as follows: repetition time (TR)/echo time (TE)/flip angle, infinite/92 ms/150°; parallel acquisition factor, 2; slice thickness, 5 mm; distance factor, 20%; transverse and coronal orientations (matrix sizes, 380 × 256 and 400 × 320, respectively); and acquisition time, approximately 90 s. A volumetric interpolated breath-hold examination sequence was used for fast T1-weighted imaging. Sequence parameters were as follows: TR/TE, 5.12 ms/2.51 ms; flip angle, 10°; partition thickness, 5 mm with no interslice gap; and matrix size, 256 × 116 (a three-dimensional breath-hold sequence being used). A T2-weighted fat-saturated periodically rotated overlapping parallel lines with enhanced reconstruction sequence (BLADE; Siemens Healthineers) was also used, sequence parameters being as follows: TR/TE, 4,670 ms/113 ms; and partition thickness, 5 mm with no interslice gap. Diffusion-weighted imaging was performed with the use of a single-shot echo-planar technique, a slice thickness of 6 mm, spectral attenuated inversion recovery, and respiratory-triggered scanning being used. Sequence parameters were as follows: TR/TE/flip angle, 3,000-4,500 ms/65 ms/90°; diffusion gradient encoding in three orthogonal directions; b = 50, 400, and 800 s/mm^2; field of view, 350 mm; and matrix size, 128 × 128. The mean overall time spent in the MR imaging room was approximately 15 min, and no sedation was required.

Image analysis

The CT scans and MR images were independently reviewed by two chest radiologists who had more than 7 years of experience and who were blinded to patient clinical information. Subsequently, the two radiologists together reviewed the scans and images in order to make a final consensus decision. The criteria for CT and MR imaging findings were those defined in the Fleischner Society Glossary of Terms.[19]

During CT analysis, the chest radiologists identified areas of calcification in a mediastinal window, measuring mean density within a region of interest (ROI) that included at least 90% of the calcification identified on CT. Subsequently, thoracic calcifications were classified as diffuse (diffuse or patchy areas of bone-like calcification), punctate (micronodular areas of bone-like calcification), or laminar (linear areas of bone-like calcification). All scans were reviewed on a dedicated workstation (Advantage Workstation 4.2; GE Healthcare), a picture archiving and communication system being used.

MR images were semiquantitatively analyzed by the aforementioned radiologists, who manually defined three-dimensional ROIs by compounding two-dimensional lesion boundaries drawn on consecutive sections, the calcifications seen on CT being used as reference. In addition, an ROI was drawn in the paraspinal muscle at the same level on axial T1- and T2-WIs (mean area, 50-80 mm^2, i.e., 14-30 pixels), and the lesion-to-muscle signal intensity ratio (LMSIR) was estimated. An LMSIR of

< 1 characterized a hypointense lesion, an LMSIR = 1 characterized an isointense lesion, an LMSIR > 1 characterized a hyperintense lesion, and an LMSIR = 0 characterized a lesion that was undetectable by MR imaging (null effect).

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations or medians and interquartile ranges (IQRs), whereas categorical variables were expressed as absolute numbers and proportions. Continuous variables with normal distribution were compared by the Student's t-test for independent samples, whereas continuous variables with non-normal distribution were compared by the Mann-Whitney U test. Categorical variables were compared by Fisher's exact test. The level of significance was set at $p < 0.05$.

Pearson's correlation coefficients were used in order to assess correlations between continuous variables, coefficients of 0.00-0.20 indicating a very weak correlation, coefficients ≥ 0.20-0.40 indicating a weak correlation, coefficients ≥ 0.40-0.70 indicating a moderate correlation, coefficients ≥ 0.70-0.90 indicating a strong correlation, and coefficients ≥ 0.90 indicating a very strong correlation.[20]

RESULTS

The study sample consisted of 62 patients (84 calcified lesions). Of those 62 patients, 37 (59.7%) were female. Mean ROI size was 22 mm^2 (8-49 mm^2). Of the 84 lesions, 46 (54.8%) were solitary. Of the 62 patients in the study sample, 36 had participated in a study comparing CT and MR imaging in the assessment of lung nodules, 18 had participated in a study comparing CT and MR imaging in the assessment of pulmonary vessels, and 8 had participated in a study comparing CT and MR imaging for lung cancer staging.

Mean lesion density on CT was 367 ± 435 HU. Of the 84 lesions analyzed, 56 (66.7%) were pulmonary lesions, 5 (5.9%) were pleural lesions, and 23 (27.4%) were mediastinal lesions. In addition, 65 (77.4%) were diffuse, 15 (17.8%) were laminar, and 4 (4.8%) were punctate. Median LMSIRs on T1- and T2-WIs were 0.4 (IQR, 0.1-0.7) and 0.2 (IQR, 0.0-0.7), respectively.

Most of the lesions were hypointense on T1- and T2-WIs (n = 52 [61.9%] and n = 39 [46.4%], respectively). In addition, 19 (22.6%) were undetectable on T1-WIs (LMSIR = 0) and 36 (42.9%) were undetectable on T2-WIs (LMSIR = 0). Finally, 15.5% were hyperintense on T1-WIs and 9.5% were hyperintense on T2-WIs (Figure 1).

As can be seen in Table 1, there was a significant difference between neoplastic and non-neoplastic lesions regarding minimum lesion diameter and maximum lesion diameter ($p < 0.05$). Although neoplastic and non-neoplastic lesions were hypointense on T1- and T2-WIs, median LMSIR was significantly higher for the former than for the latter (Table 1). Although all of the neoplastic lesions were detectable by MR imaging (Figures 1 and 2), 25% and 47.4% of the non-neoplastic lesions were undetectable on T1- and T2-WIs, respectively (Table 1).

Table 2 shows LMSIRs on T1- and T2-WIs, by calcification type. Most of the diffuse calcifications were either hypointense or undetectable on T1- and T2-WIs. Most of the laminar calcifications were hypointense, and all showed signal intensity on T1- and T2-WIs.

There was a very weak and statistically insignificant negative correlation between lesion density on CT and the following variables: signal intensity on T1-WIs, LMSIR on T1-WIs, and signal intensity on T2-WIs ($r = -0.13$, $p = 0.24$; $r = -0.18$, $p = 0.10$; and $r = -0.16$, $p = 0.16$, respectively). In addition, lesion density on CT was weakly but significantly correlated with LMSIR on T2-WIs ($r = -0.29$, $p < 0.05$).

DISCUSSION

The present study showed that thoracic calcifications have variable signal intensity on T1- and T2-weighted MR images. The chemical composition of calcifications includes crystalline calcium phosphate and hydroxyapatite, as well as a small quantity of copper, manganese, zinc, magnesium, and iron.[8] The fact that the concentrations vary in different physiological

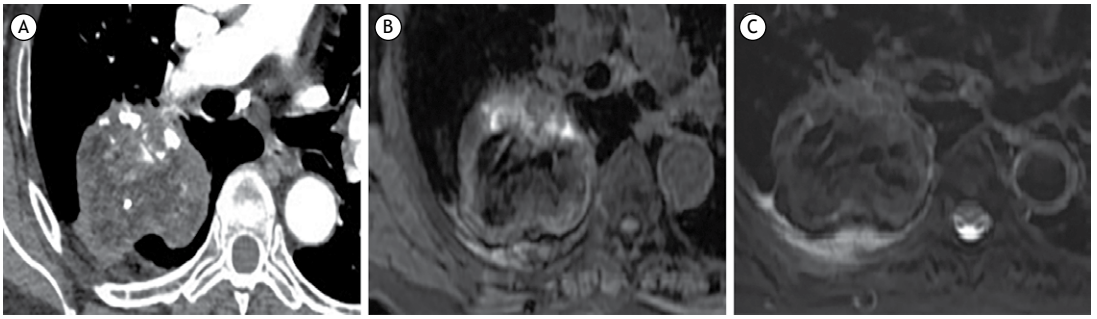

Figure 1. In A, axial CT scan of the chest (mediastinal window) showing calcification within a large lesion in the right lower lobe. In B and C, magnetic resonance imaging of the calcification seen on CT. Note that the lesion is hyperintense on T1- and T2-weighted images (B and C, respectively).

Table 1. Magnetic resonance imaging features of neoplastic and non-neoplastic lung lesions.[a]

Variable	Neoplastic lesions (n = 8)	Non-neoplastic lesions (n = 76)	p*
Lesion diameter, mm			
Minimum diameter	6.49 ± 7.72	1.85 ± 2.75	< 0.05
Maximum diameter	11.35 ± 13.20	3.67 ± 4.96	< 0.05
LMSIR on T1-WIs[b]	0.9 [0.7-1.1]	0.4 [0.1-0.6]	< 0.05
Undetectable lesion (LMSIR = 0)[c]	-	19 (25)	
Hypointense lesion (LMSIR < 1)[c]	5 (62.5)	47 (61.8)	-
Isointense lesion (LMSIR = 1)[c]	-	4 (5.3)	-
Hyperintense lesion (LMSIR > 1)[c]	3 (37.5)	6 (7.9)	-
LMSIR on T2-WIs[b]	0.9 [0.4-1.3]	0.1 [0.0-0.6]	< 0.05
Undetectable lesion (LMSIR = 0)[c]	-	36 (47.4)	
Hypointense lesion (LMSIR < 1)[c]	4 (50.0)	34 (44.7)	-
Isointense lesion (LMSIR = 1)[c]	1 (12.5)	2 (2.6)	-
Hyperintense lesion (LMSIR > 1)[c]	3 (37.5)	4 (5.3)	-

LMSIR: lesion-to-muscle signal intensity ratio; T1-WIs: T1-weighted images; and T2-WIs: T2-weighted images. [a]Data expressed as mean ± SD, except where otherwise indicated. [b]Data expressed as median [interquartile range]. [c]Data expressed as n (%). *Mann-Whitney U test.

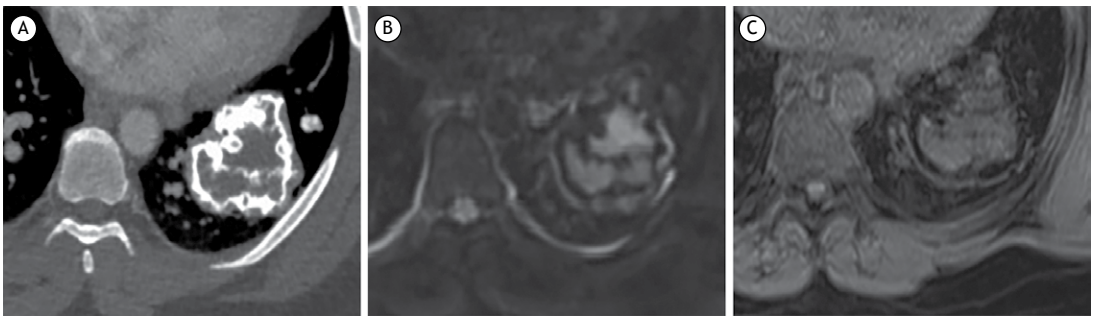

Figure 2. In A, axial CT scan of the chest (mediastinal window) showing a large lesion with associated calcifications in the left lower lobe. In B, axial T2-weighted image showing that the calcifications have a markedly lower signal intensity than that of skeletal muscle. In C, axial T1-weighted image showing hypointense calcifications within the lesion.

Table 2. Lesion-to-muscle signal intensity ratios on T1- and T2-weighted images, by calcification type.[a]

Variable	Diffuse calcifications (n = 65)	Punctate calcifications (n = 4)	Laminar calcifications (n = 15)
LMSIR on T1-WIs	0.3 [0.0-0.5]	0.7 [0.5-0.9]	0.6 [0.5-0.9]
Undetectable lesion (LMSIR = 0)[b]	18 (27.7)	1 (25.0)	-
Hypointense lesion (LMSIR < 1)[b]	39 (60.0)	2 (50.0)	11 (73.3)
Isointense lesion (LMSIR = 1)[b]	-	-	-
Hyperintense lesion (LMSIR > 1)[b]	8 (12.3)	1 (25.0)	4 (26.7)
LMSIR on T2-WIs	0.0 [0.0-0.6]	0.6 [0.1-1.3]	0.7 [0.4-0.9]
Undetectable lesion (LMSIR = 0)[b]	35 (53.8)	1 (25.0)	-
Hypointense lesion (LMSIR < 1)[b]	26 (40.0)	1 (25.0)	12 (80.0)
Isointense lesion (LMSIR = 1)[b]	-	-	1 (6.7)
Hyperintense lesion (LMSIR > 1)[b]	4 (6.2)	2 (50.0)	2 (13.3)

LMSIR: lesion-to-muscle signal intensity ratio; T1-WIs: T1-weighted images; and T2-WIs: T2-weighted images. [a]Data expressed as median [interquartile range], except where otherwise indicated. [b]Data expressed as n (%).

and pathological calcifications might explain their heterogeneous appearance on MR images.[8] It has been suggested that this variation in appearance is due to a surface-relaxation mechanism, which reduces T1 and T2 relaxation times.[6] It has been demonstrated that materials that have the same size and chemical composition can have markedly different effects on relaxation depending on the degree of irregularity of the surface.[6,8] The inherent properties of calcium can cause hyperintensity on T1-WIs. The T1 effect predominates in cases in which the surface is very irregular and the surface area is very large—as is the case with calcium crystals—increasing MR signal intensity.[6] This might explain why the proportion of hyperintense lesions was higher on T1-WIs than on T2-WIs in the present study.

As the calcium concentration increases above 30-40%, proton density decreases, thus resulting in a progressive decrease in signal intensity.[6] The fact that calcified lesions appear hypointense on MR images has been attributed to decreased proton density.[6-10] In the present study, a negative but statistically insignificant correlation was found between lesion density on CT and lesion signal intensity on MR images, corroborating the finding that lesions with increased calcium concentration tend to have decreased signal intensity on MR images. This could also explain why median LMSIRs on T1- and T2-WIs were lower for diffuse calcifications than for punctate and laminar calcifications.

Previous studies have described neoplastic calcifications appearing hyperintense on MR images.[7,8,10,21] In the present study, neoplastic calcifications had a variable appearance on MR images. However, median LMSIR was significantly higher for hyperintense lesions than for hypointense lesions (37.5% vs. 7.9% on T1-WIs and 37.5% vs. 5.3% on T2-WIs). This might be due to low calcium concentrations changing the surface effects of diamagnetic particles on the MR signal and resulting in T1 shortening of water protons.

Our study has limitations, some of which are inherent to its retrospective nature. Larger, prospective studies are needed in order to confirm the findings of our subgroup analysis. In addition, future studies should include imaging sequences other than conventional spin-echo T1- and T2-weighted sequences.

Technical challenges to successful MR imaging of the lung include low tissue density (resulting in decreased signal intensity) and magnetic susceptibility differences between tissue and air.[22] Some studies have used gradient-echo MR imaging and quantitative susceptibility mapping in order to characterize calcified brain lesions. [7] Susceptibility-weighted imaging (SWI) is useful for differentiating between intracranial calcifications and hemorrhages, which can have similar attenuation on CT scans.[7] To our knowledge, however, there have been no studies examining the use of SWI in MR imaging of the chest.

Another limitation of our study is the use of a mean signal intensity within a predefined ROI. Signal intensity has been reported to vary throughout a calcified lesion (e.g., a hyperintense periphery and decreased intensity toward the center).[6] However, we believe that this has little impact on clinical practice.

In conclusion, thoracic calcifications (particularly neoplastic calcifications) have variable signal intensity on T1- and T2-weighted MR images, and lesion density on CT appears to correlate negatively with lesion signal intensity on MR images. Radiologists should be aware of these findings when interpreting chest MR images.

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ORIGINAL ARTICLE

Do N-terminal pro-brain natriuretic peptide levels determine the prognosis of community acquired pneumonia?

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ABSTRACT

Objective: Pneumonia is a leading cause of mortality worldwide, especially in the elderly. The use of clinical risk scores to determine prognosis is complex and therefore leads to errors in clinical practice. Pneumonia can cause increases in the levels of cardiac biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP). The prognostic role of the NT-proBNP level in community acquired pneumonia (CAP) remains unclear. The aim of this study was to evaluate the prognostic role of the NT-proBNP level in patients with CAP, as well as its correlation with clinical risk scores. **Methods:** Consecutive inpatients with CAP were enrolled in the study. At hospital admission, venous blood samples were collected for the evaluation of NT-proBNP levels. The Pneumonia Severity Index (PSI) and the **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years (CURB-65) score were calculated. The primary outcome of interest was all-cause mortality within the first 30 days after hospital admission, and a secondary outcome was ICU admission. **Results:** The NT-proBNP level was one of the best predictors of 30-day mortality, with an area under the curve (AUC) of 0.735 (95% **CI:** 0.642-0.828; $p < 0.001$), as was the PSI, which had an AUC of 0.739 (95% **CI:** 0.634-0.843; $p < 0.001$), whereas the CURB-65 had an AUC of only 0.659 (95% **CI:** 0.556-0.763; $p = 0.006$). The NT-proBNP cut-off level found to be the best predictor of ICU admission and 30-day mortality was 1,434.5 pg/mL. **Conclusions:** The NT-proBNP level appears to be a good predictor of ICU admission and 30-day mortality among inpatients with CAP, with a predictive value for mortality comparable to that of the PSI and better than that of the CURB-65 score.

Keywords: Pneumonia/diagnosis; Pneumonia/mortality; Natriuretic peptide, brain; Community-acquired infections.

INTRODUCTION

Despite recent developments in clinical care and antimicrobial treatment, pneumonia continues to be a leading cause of mortality worldwide, especially in the elderly. In cases of community-acquired pneumonia (CAP), the Pneumonia Severity Index (PSI) and the **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years (CURB-65) score are used in order to predict the severity and determine the prognosis.[1,2] However, calculating risk scores, especially the PSI, is complex and is dependent on subjective impressions, which can lead to errors in clinical practice.[3] Brain natriuretic peptide (BNP) is a potent natriuretic and diuretic hormone that is released from the heart into the systemic circulation and is enzymatically cleaved into active and inactive forms—BNP and N-terminal pro-brain natriuretic peptide (NT-proBNP), respectively. The optimal timing of NT-proBNP assessment for risk stratification is unclear. Weber et al.[4] showed that, to determine the peak elevation of NT-proBNP, it is necessary to perform sequential testing, the second sample being collected 24-36 h after the onset of symptoms of acute coronary syndrome. However, it remains an open issue whether the peak values of NT-proBNP are of superior predictive value. The levels of BNP and NT-proBNP are elevated in cases of increased myocardial strain. In patients with cardiac failure, the NT-proBNP level can be measured rapidly with a simple method. Pneumonia can also cause an increase in the levels of cardiac biomarkers.[5,6]

As compared with BNP, NT-proBNP has a number of advantages, including a longer half-life and higher in vitro stability.[7] Although previous studies have suggested that BNP and NT-proBNP levels are useful for risk stratification and for determining the prognosis in patients with CAP,[8,9] the prognostic role of the NT-proBNP level in CAP remains unclear. The aim of this study was to evaluate the prognostic role of the NT-proBNP level in patients with CAP by investigating its association with 30-day mortality, ICU admission, length of hospital stay, and clinical risk scores (PSI and CURB-65 score).

METHODS

This was a prospective study in which consecutive patients who were hospitalized for CAP between March 2014 and October 2018 were enrolled. The study protocol

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was approved by the local research ethics committee, and all participating patients gave written informed consent.

The inclusion criteria were as follows: being ≥ 18 years of age; having a fever (≥ 37.3°C); presenting with cough of recent onset, sputum production, or other symptoms of respiratory infection, including purulent sputum, with or without chest pain; having a leukocyte count > 10×10^9/L or < 4×10^9/L; and showing patchy infiltrative shadows or interstitial changes, with or without effusion, on chest X-rays. Patients with active tuberculosis, lung cancer, pulmonary fibrosis, pulmonary embolisms, pulmonary hypertension, or nosocomial pneumonia were excluded, as were those with congestive heart failure, cirrhosis, acute coronary syndrome, end-stage renal disease, or acute kidney injury.

The levels of NT-pro-BNP were assessed with the Elecsys-ProBNP assay (Roche Diagnostics, Penzberg, Germany). The assay uses two polyclonal antibodies, one of which is labeled with ruthenium complex and measures the inactive cleavage product of BNP (i.e., NT-pro-BNP). It also includes an automated electrochemiluminescence immunoassay. The Elecsys immunoassay analyzer (Roche Diagnostics) provides the initial results in 18 min. Two cut-off points are used, one at 125 pg/mL, for patients < 75 years of age, and the other at 450 pg/mL, for patients ≥ 75 years of age.[10] High-sensitivity C-reactive protein levels were measured by automatic calorimetric assay in a COBAS INTEGRA 400 plus analyzer (Roche Diagnostics, Mannheim, Germany), with a cut-off level of 5 μg/L.

The medical histories and demographic characteristics of the patients were recorded. At admission, vital signs, complete blood counts, serum glucose levels, liver function, kidney function, and arterial blood gases were assessed. A chest X-ray was also obtained. The PSI and CURB-65 scores of the patients were calculated in accordance with the American Thoracic Society guidelines.[1] The need for ICU admission was determined on the basis of the criteria established by the Infectious Diseases Society of America and the American Thoracic Society guidelines for CAP.[11] Acute physiology and chronic health evaluation II (APACHE II) scores were calculated for patients admitted to the ICU.[12]

To exclude cardiac causes of myocardial strain, such as congestive heart failure, we performed electrocardiography and transthoracic echocardiography at admission. Echocardiographic measurements were performed on a ViVid 7 Pro system (GE Vingmed, Horten, Norway) with a 1.7 MHz transducer that was capable of harmonic imaging. Conventional echocardiography and tissue Doppler imaging were performed by two cardiologists who were blinded to the clinical status of the subjects. Pulmonary hypertension was defined as a systolic pulmonary arterial pressure > 35 mmHg, and left ventricular systolic dysfunction was defined as an ejection fraction < 50%.[13,14]

The primary outcome of interest was all-cause mortality within the first 30 days after hospital admission. Secondary outcomes were ICU admission and the length of the hospital stay.

Statistical analysis

The statistical analysis was performed with the SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA). To identify the risk factors for ICU admission and 30-day mortality, we performed univariate and multivariate logistic regression analyses. In the multivariate logistic regression models, backward logistic regression was used and the criterion for inclusion of the candidate variables in the model was a $p < 0.25$. Multivariate linear regression models were used for continuous response variables such as length of hospital stay. The prognostic performance of parameters such as the CURB-65, the PSI, and SpO_2 was compared by using ROC curve analysis. The results are summarized as the area under the curve (AUC), with 95% confidence intervals and standard errors. In addition, the optimal cut-off points were calculated by using the Youden index. For group comparisons, normal distribution was assessed with the Shapiro-Wilk test, continuous variables were assessed with Student's t-tests or Mann-Whitney U tests, and categorical variables were assessed with chi-square tests or Fisher's exact tests. The relationships between variables such as the CURB-65 score, PSI, APACHE II score, and NT-proBNP level were examined with Spearman's correlation coefficients. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Initially, 179 patients were considered for inclusion in the study. On the basis of the study criteria, 24 of those patients were excluded for presenting with one of the following comorbidities: active tuberculosis (n = 1); lung cancer (n = 3); pulmonary fibrosis (n = 2); pulmonary embolism (n = 2); pulmonary hypertension (n = 1); nosocomial pneumonia (n = 2); congestive heart failure (n = 4); cirrhosis (n = 1); acute coronary syndrome (n = 3); end-stage renal disease (n = 3); and acute kidney injury (n = 2). Therefore, 155 patients were enrolled in the study. Of those 155 patients, 54 (34.8%) were female and 101 (65.2%) were male. The mean age of the patients was 72.70 ± 12.64 years. The gender distribution, smoking status, PSI, CURB-65 scores, mortality rates, and ICU admission rates are shown in Table 1.

The univariate analysis showed that the factors influencing ICU admission and 30-day mortality were the PSI ($p < 0.001$ for both), CURB-65 score ($p < 0.001$ and $p = 0.002$, respectively), serum NT-proBNP level ($p < 0.001$ and $p = 0.023$, respectively), and leukocyte count ($p = 0.034$ and $p = 0.024$, respectively). Multivariate logistic regression analysis showed that the PSI and CURB-65 score were both predictive of 30-day mortality. According to the univariate analysis, the factors that affected the length of hospital stay were

the CURB-65 score, serum NT-proBNP level, albumin level, leukocyte count, and SpO_2 ($p < 0.001$, $p < 0.001$, $p = 0.020$, and $p = 0.024$, respectively). Table 2 shows the results of the univariate and multivariate logistic regression analyses of the potential predictors of 30-day mortality.

As can be seen in Figure 1, the mean NT-proBNP level was significantly higher among the patients who died within the first 30 days after hospital admission than among those who survived (4,594.41 ± 6,993.71 pg/mL vs. 1,759.98 ± 3,589.21 pg/mL; $p = 0.002$). The mean NT-proBNP level was also significantly higher among the patients who were admitted to the ICU than among those who were not (5,209.50 ± 7,807.21 pg/mL vs. 1,255.44 ± 1,562.32 pg/mL; $p < 0.001$).

When we employed Spearman's correlation coefficients to examine the simple correlations, we found a significant correlation between the NT-proBNP level and the PSI ($r = 0.441$; $p < 0.001$). The PSI also correlated significantly with the CURB-65 score ($r = 0.318$; $p < 0.001$). The simple correlations among the NT-proBNP level, PSI, CURB-65 score, and APACHE II score are shown in Table 3.

A ROC curve showed that the PSI, NT-proBNP level, and CURB-65 score all had predictive value for 30-day mortality. The PSI and NT-proBNP level had similar predictive values for 30-day mortality, both of which were better than that of the CURB-65 score. The AUCs for the PSI, NT-proBNP level, and CURB-65 score, respectively, were as follows (Figure 2): 0.739 (95% CI: 0.634-0.843; $p < 0.001$); 0.735 (95% CI: 0.642-0.828; $p < 0.001$); and 0.659 (95% CI: 0.556-0.763; $p = 0.006$). The best NT-proBNP cut-off level for the prediction of ICU admission and 30-day mortality was found to be 1,434.5 pg/mL, which had a sensitivity and specificity of 0.738 and 0.735, respectively, for ICU admission, compared with 0.710 and 0.685, respectively, for 30-day mortality.

The ROC analysis was performed with the probabilities obtained from two different logistic models for the prediction of mortality: one including the PSI only and one including the PSI and the NT-proBNP level together. The addition of the NT-proBNP level to the PSI increased the predictive value for 30-day mortality. Figure 3 shows the ROC curves constructed from the predicted probabilities of the PSI as a single variable and of the PSI in combination with the NT-proBNP level—designated PSI + log(proBNP)—for the prediction of 30-day mortality. The AUC for the PSI was 0.772 (95% CI: 0.682-0.861), with an SE of 0.046 ($p < 0.001$), whereas the AUC for the PSI + log(proBNP)

Table 1. Gender distribution, smoking status, clinical risk scores, ICU admission rates, and mortality rates among inpatients with community-acquired pneumonia (N = 155).

Variable	n (%)
Gender	
Female	54 (34.8)
Male	101 (65.9)
Smoking status	
Never smoker	68 (43.9)
Current smoker	23 (14.8)
Former smoker	64 (41.3)
PSI	
1	2 (1.3)
2	22 (14.2)
3	72 (46.5)
4	54 (34.8)
5	5 (3.2)
CURB-65 score	
0	7 (4.5)
1	25 (16.1)
2	58 (37.4)
3	56 (36.1)
4	8 (5.2)
5	1 (0.6)
ICU admission	
Yes	42 (27.1)
No	113 (72.9)
30-day mortality	
Yes	31 (20.0)
No	124 (80.0)

PSI: Pneumonia Severity Index; and CURB-65: **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years.

Table 2. Results of the univariate and multivariate logistic regression analyses of the potential predictors of 30-day mortality.

Variable	β	SE	OR	95% CI	p
Univariate analysis					
PSI	1.317	0.335	3.733	1.93-7.19	< 0.001
CURB-65 score	0.804	0.253	2.234	1.35-3.67	0.002
CRP	0.219	0.228	1.245	0.79-1.94	0.336
Leukocyte count*	0.000	0.000	1.000	1.00-1.10	0.024
NT-proBNP level**	0.113	0.050	1.120	1.01-1.23	0.023
Multivariate analysis					
PSI	1.145	0.351	3.143	1.58-6.25	0.001
CURB-65 score	0.550	0.267	1.733	1.02-2.92	0.040

PSI: Pneumonia Severity Index; CURB-65: mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years; CRP: C-reactive protein; and NT-proBNP: N-terminal pro-brain natriuretic peptide. *100 times the exact measure. **1,000 times the exact measure.

variable was 0.812 (95% CI: 0.727-0.897), with an SE of 0.043 ($p < 0.001$).

DISCUSSION

The main finding of the present study was that the NT-proBNP level correlated significantly with the PSI and CURB-65 score in terms of the mean length of hospital stay and the prediction of mortality. The NT-proBNP level was one of the best predictors of mortality. The NT-proBNP level also correlated significantly with the CURB-65 score in patients admitted to the ICU. The best NT-proBNP cut-off level for the prediction of ICU admission and 30-day mortality was 1,434.5 pg/mL. The combination of the NT-proBNP level and the PSI had a better predictive value for 30-day mortality than did the PSI alone.

The PSI and CURB-65 are risk scoring systems used in evaluating the severity of CAP. However, they play a limited role in determining the prognosis of CAP. It was previously shown that the PSI and CURB-65 score both markedly underestimated mortality, particularly in the low-risk strata. That leads to the misclassification of patients with substantial mortality in the low-risk strata.[15] The CURB-65 score and PSI have both been shown to have low predictive specificity, incorrectly categorizing many young patients as being at low risk.[16] The present study showed that the PSI and CURB-65 score both had predictive value for mortality. Because our study population included only inpatients with CAP, most of the patients were in the high-risk strata and were elderly (mean age, 72.70 years). Those properties might have had a preventive effect against underestimation of mortality in the low-risk strata and young patients. In addition, the calculation of the PSI is complicated and its use is therefore not feasible in clinical practice, especially in the emergency department. Although the CURB-65 scoring system is simpler than is that of the PSI, the former has lower sensitivity for the prediction of 30-day mortality.[16,17] In a study of the role of the BNP level in predicting the severity of CAP, Li et al.[18] showed that it correlated positively with the severity of CAP, which is in accordance with the findings of the present study. In their study, the best BNP cut-off level for predicting mortality was found to be 299 pg/mL, which had good sensitivity and even better specificity. Usuda et al.[8] also studied the prognostic role of the BNP level in patients with pneumonia and found that a high BNP level (≥ 200 pg/mL) at admission was a predictor of CAP-related death.[8] In patients with cardiac or renal dysfunction, the

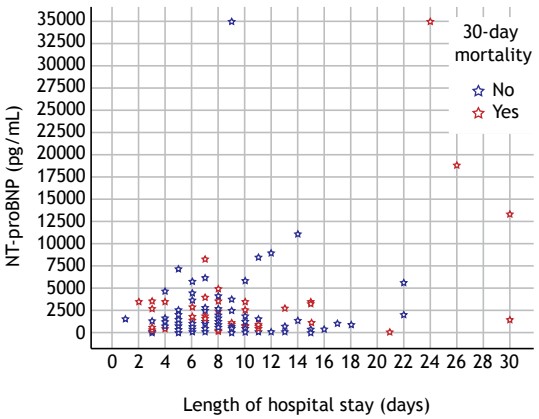

Figure 1. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) among patients with community-acquired pneumonia who died within the first 30 days after hospital admission and among those who survived.

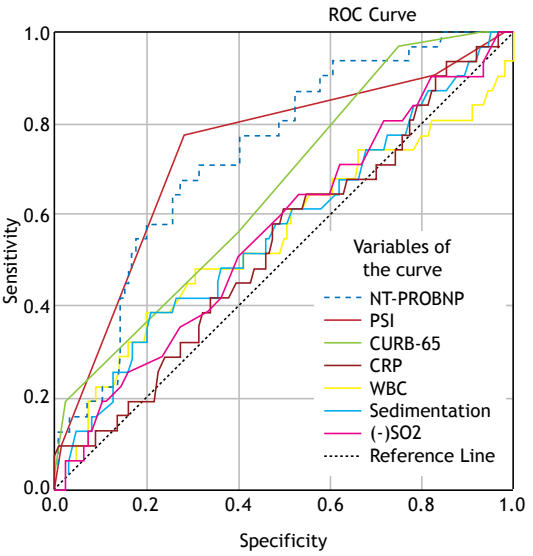

Figure 2. The ROC curve for potential predictors of 30-day mortality. The areas under the ROC curve were as follows: 0.739 (95% CI: 0.634-0.843) for the Pneumonia Severity Index (PSI; $p < 0.001$); 0.735 (95% CI: 0.642-0.828) for the N-terminal pro-brain natriuretic peptide (NT-proBNP) level ($p < 0.001$); and 0.659 (95% CI: 0.556-0.763) for the **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years (CURB-65) score ($p = 0.006$). CRP: C-reactive protein.

Table 3. Simple correlation coefficients among selected variables.

Variable	PSI	CURB-65 score	APACHE II score
	Spearman's rho (p)	Spearman's rho (p)	Spearman's rho (p)
NT-proBNP level	0.441 (< 0.001)	0.086 (0.286)	0.113 (0.475)
PSI	-	0.318 (< 0.001)	0.241 (0.124)
CURB-65 score		-	0.103 (0.514)
APACHE II score			-

NT-proBNP: N-terminal pro-brain natriuretic peptide; PSI: Pneumonia Severity Index; CURB-65: mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age ≥ **65** years; and APACHE II: Acute Physiology and Chronic Health Evaluation II.

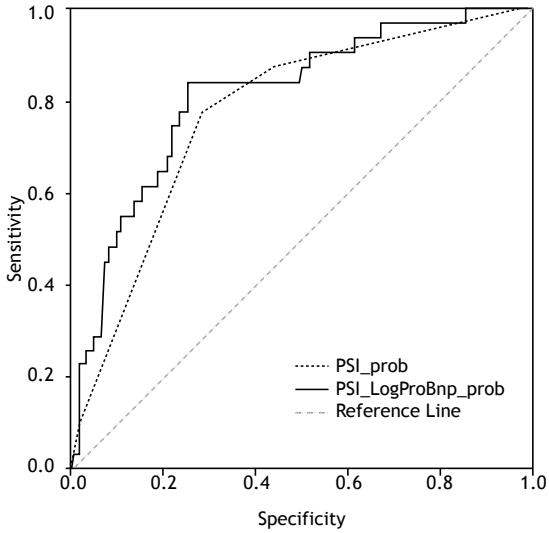

Figure 3. The ROC curves constructed from the predicted probabilities of the PSI as a single variable and of the PSI in combination with the NT-proBNP level—designated PSI + log(proBNP)—for the prediction of 30-day mortality. The AUC for the PSI was 0.772 (95% CI: 0.682-0.861), with an SE of 0.046 ($p < 0.001$), whereas the AUC for the PSI + log(proBNP) variable was 0.812 (95% CI: 0.727-0.897), with an SE of 0.043 ($p < 0.001$).

level of NT-proBNP rises more steeply than does that of BNP. Furthermore, in comparison with BNP, NT-proBNP is larger, is detected more rapidly, is more biologically stable, and has a longer half-life.[19,20] Therefore, we opted to measure NT-proBNP, rather than BNP, in the present study. As previously mentioned, we found the best NT-proBNP cut-off level for the prediction of ICU admission and 30-day mortality to be 1,434.5 pg/mL, which had good sensitivity and specificity for both outcome measures.

Jeong et al.[21] showed that the NT-proBNP levels of patients with CAP who died were significantly higher than were those of survivors.[21] Our results support that finding, the NT-proBNP levels of our patients who died within the first 30 days after hospital admission being significantly higher than were those of the patients who survived. We also evaluated the relationship between ICU admission and NT-proBNP levels, finding that the NT-proBNP levels of the patients who were admitted to the ICU were significantly higher than were those of the patients who did not require ICU admission.

Lin et al.[22] investigated the plasma levels of NT-proBNP at ICU admission and 30-day mortality in patients with pneumonia, healthcare-associated pneumonia accounting for 40% of the sample, whereas CAP and hospital-acquired pneumonia accounted for 35% and 25%, respectively. Those authors also found that the mean NT-proBNP levels were significantly lower among the survivors than among the nonsurvivors. They also reported that the NT-proBNP level showed prognostic accuracy comparable to that of the APACHE II score in patients who were admitted to the ICU with pneumonia. However, although the NT-proBNP levels correlated significantly with the CURB-65 score in patients admitted to the ICU in the present study, there was no correlation between those levels and the APACHE II scores in those same patients.

Nowak et al.[9] suggested that the levels of natriuretic peptides, especially NT-proBNP, could predict mortality in CAP and that their predictive ability is comparable to that of the PSI.[9] Consistent with that idea, we found that the predictive value of the NT-proBNP level was comparable to that of the PSI and that the former was a more powerful predictor than was the CURB-65 score. Although the PSI is a validated tool, it includes many parameters related to demographic characteristics, comorbidities, and laboratory findings, as well as being partially dependent on subjective impressions. In contrast, the measurement of the NT-proBNP level is simple and objective. Therefore, it could be an alternative to the PSI for predicting the severity and determining the prognosis of CAP. In addition, our study showed that combining the NT-proBNP level and the PSI increased the predictive value for 30-day mortality over that of the PSI alone.

The mechanism of myocardial strain, which increases the levels of cardiac biomarkers in patients with pneumonia, is not clear. Musher et al.[23] found a myocardial infarction rate of 7-8% among patients who were hospitalized for pneumonia. The risk of myocardial infarction associated with pneumonia peaks at the onset of infection and is proportional to the severity of the pneumonia.[24] In the present study, we excluded patients who had comorbidities that can affect the NT-proBNP level, such as acute coronary syndrome, in order to avoid the confounding effects of such comorbidities. CAP places significant stress on the cardiovascular system via the induction of low peripheral vascular resistance, increased cardiac output, and the occurrence of arteriovenous shunts in areas of inflammation.[9] Studies in patients with sepsis have suggested that cardiac biomarker levels reflect the extent of systemic inflammation.[23,25] Zhang et al.[26] found that the NT-proBNP levels of patients with pneumonia correlated positively with inflammatory markers, such as the leukocyte count, ESR, and C-reactive protein level. Among the biochemical parameters evaluated in the present study, the consistent predictors of ICU admission and 30-day mortality included not only the NT-proBNP level but also the leukocyte count. However, we did not detect any relationships between mortality and other inflammatory markers, such as the C-reactive protein level and the ESR.

The present study has several limitations. First, the study population consisted only of inpatients with CAP, most of whom were elderly. In addition, patients who had comorbidities that could affect the NT-proBNP level were excluded from the study. Therefore, it might not be possible to extrapolate our findings to the general population of patients with CAP. Second, this was a single-center study conducted at a university hospital. Multicenter studies of patients with CAP might help clarify the prognostic role of the NT-proBNP level.

In conclusion, the NT-proBNP level appears to be a good predictor of ICU admission and short-term mortality among patients hospitalized for CAP. We found its predictive value for mortality to be comparable to that of the PSI and better than that of the CURB-65 score. We also found that the inclusion of the NT-proBNP level increased the predictive value of PSI for mortality. There is a need for population-based randomized controlled studies in order to determine the exact prognostic role that the NT-proBNP level plays in CAP and to validate NT-proBNP as a prognostic marker in the general population of patients with CAP.

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Effect of vaporized perfluorocarbon on oxidative stress during the cold ischemia phase of lung graft preservation

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ABSTRACT

Liquid perfluorocarbon (PFC) instillation has been studied experimentally as an adjuvant therapy in the preservation of lung grafts during cold ischemia. The objective of this study was to evaluate whether vaporized PFC is also protective of lung grafts at different cold ischemia times. We performed histological analysis of and measured oxidative stress in the lungs of animals that received only preservation solution with low-potassium dextran (LPD) or vaporized PFC together with LPD. We conclude that vaporized PFC reduces the production of free radicals and the number of pulmonary structural changes resulting from cold ischemia.

Keywords: Ischemia; Reperfusion; Fluorocarbons; Lung transplantation; Oxidative stress.

Various methods and substances to improve lung graft preservation during cold ischemia, such as pulmonary surfactant, liquid perfluorocarbon (PFC), complement inhibitors, and nitrites, as well as inhalation of hydrogen sulfide or nitric oxide, have been tested experimentally.[1,2] However, the standard method of lung graft preservation is still perfusion with a cold low-potassium dextran (LPD) solution via the pulmonary artery (antegrade perfusion) or via the pulmonary veins (retrograde perfusion), together with the use of pulmonary vasodilators and partial inflation of the lungs with oxygen during storage.[2] The use of vaporized PFC seems to be an interesting alternative in lung graft preservation, given that the use of liquid PFC has been shown to be protective of lung grafts before and after reperfusion.[3-5] The potential benefits of vaporized PFC in lung graft preservation are its ability to transport oxygen and carbon dioxide, together with its anti-inflammatory and antioxidant properties.[6-8] In addition, in its vaporized form, PFC is easily distributed throughout the lungs in a more uniform way, and, chiefly, it does not cause the ventilation difficulties observed in lungs perfused with liquid PFC. To determine the effects of vaporized PFC during lung graft preservation and to analyze oxidative stress/histological changes in lung grafts preserved for different periods of time, we used an animal model of cold ischemia. This was a controlled experimental study involving Wistar rats with a mean body weight of 300 g. All animals were treated in accordance with the World Health Organization Code of Ethics for Animal Experimentation. The animals were divided into two groups, each of which was subdivided into four groups. Each subgroup comprised six animals, depending on the surgical procedure: PFC + LPD 3h; PFC + LPD 6h; PFC + LPD 12h; and PFC + LPD 24h subgroups vs. LPD 3h; LPD 6h; LPD 12h; and LPD 24h. In the four PFC + LPD subgroups, regardless of preservation time, we used a dose of 7 mL/kg of vaporized PFC, through a tracheotomy cannula connected to an anesthesia machine, after a 120-min period of reperfusion. The animals were killed after anesthesia with ketamine (100 mg/kg, i.p.) and xylazine (50 mg/kg). Subsequently, a mid-ventral laparotomy was performed. The lungs were removed and fixed in 4% paraformaldehyde for histological analysis and were stored at −80°C for subsequent quantification of thiobarbituric acid reactive substances (TBARS), as well as for evaluation of the activity of the enzymes superoxide dismutase (SOD) and catalase. For biochemical analysis, the lung tissue was homogenized, after which protein levels were quantified as proposed by Lowry et al.[9] The levels of TBARS were measured as described by Buege and Aust,[10] and SOD activity was determined according to

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the technique described by Misra and Fridovich.[11] Catalase activity was analyzed by measuring the reduction in hydrogen peroxide levels.[12] The lung tissue samples for histological analysis were collected and stored in 10% formaldehyde solution for 12 h, after which the solution was replaced with 70% alcohol and the samples were stained with H&E. All pathology studies were performed by a pathologist who was blinded to the subgroups. Data were analyzed with IBM SPSS Statistics software, version 22.0 (IBM Corporation, Armonk, NY, USA). ANOVA followed by Tukey's post hoc test was used; in cases of unequal variance or non-normal distribution, the nonparametric Kruskal-Wallis test was performed, followed by the Mann-Whitney U test for intergroup comparisons. For all comparisons, the level of significance was set at 5%. The lungs preserved with vaporized PFC (at a dose of 7 mL/kg) + LPD for 3 and 6 h showed significantly higher SOD concentrations than did those in the LPD 3h and LPD 6h subgroups, respectively. We found no significant differences in TBARS or catalase levels among the subgroups (Figure 1).

On histology, we observed the presence of interstitial infiltrate, chronic interstitial inflammation, and atelectasis in the lungs in the LPD 3h, LPD 6h, LPD 12h, and LPD 24h subgroups, as determined by intravascular macrophage counts. In the corresponding PFC + LPD subgroups, we observed only the presence of atelectasis, which demonstrates that the use of vaporized PFC reduced pulmonary structural damage at different cold ischemia times (Figure 2).

Our results show that the use of vaporized PFC concomitantly with mechanical ventilation reduced oxidative stress during an initial cold ischemia period (for lung graft preservation) of up to 6 h, thus proving its antioxidant effect. Similar findings were obtained by Forgiarini Junior et al.,[4] who evaluated the effects of liquid PFC in a rat model of lung transplantation. In that study, the authors evaluated oxidative stress at different ischemia times and after lung transplantation, finding an increase in SOD activity but no significant differences in TBARS levels.[4] Liquid PFC has the characteristic of maintaining the alveolar structure, even after lung injury in a model of ischemia/reperfusion injury by clamping the pulmonary hilum[3] or in a model of lung transplantation.[4] Forgiarini Junior et al.[4] tested different doses of liquid PFC and demonstrated that, by using a dose of 7 mL/kg, there was better maintenance of the alveolar structure without rupture of alveolar septa. Our study demonstrated that, even in the vapor state, PFC has properties similar to those of liquid PFC in terms of protection of the alveolar structure. Although the results of our study are preliminary, to our knowledge, this is the first time that vaporized PFC has been tested as an adjuvant therapy in the preservation of lung grafts during cold ischemia. Our findings suggest that it provides protection to the alveolar structure and has antioxidant properties. Further studies are required in order to define the actual role of vaporized PFC in lung graft preservation and in the reperfusion phase after transplantation.

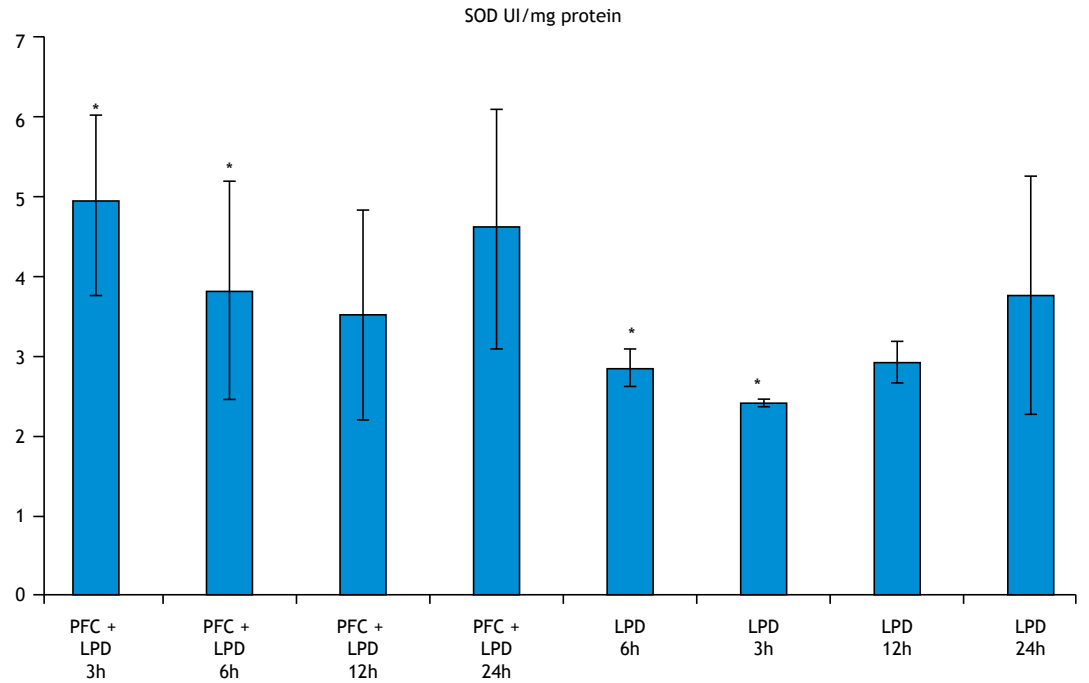

Figure 1. Comparison between the perfluorocarbon (PFC) + low-potassium dextran (LPD) subgroups and the LPD-only subgroups regarding the activity of the enzyme superoxide dismutase (SOD). Values expressed as mean ± SD. *p < 0.05 (PFC + LPD 3h vs. LPD 3h; and PFC + LPD 6h vs. LPD 6h).

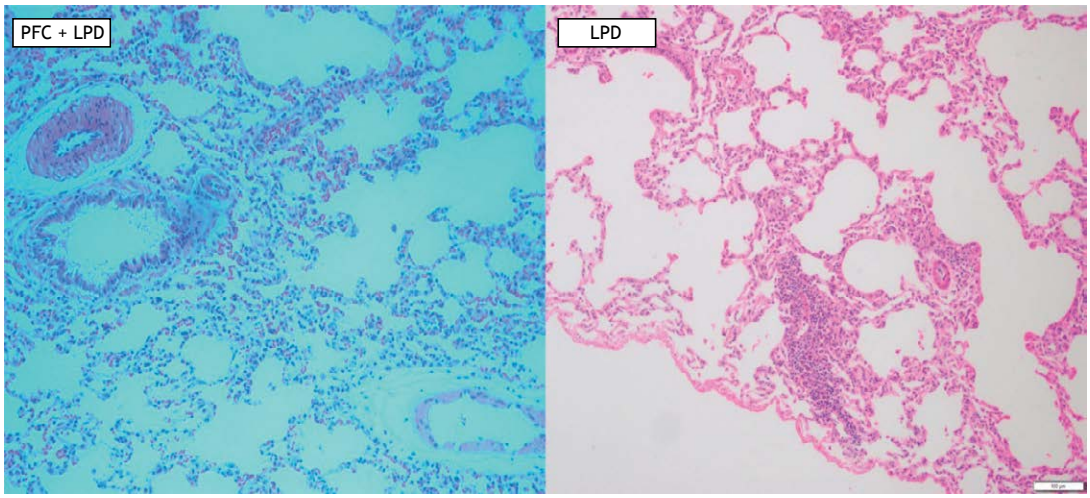

Figure 2. Photomicrographs of lung tissue samples after 24 h of cold ischemia. There is greater inflammation in the lungs that were perfused with low-potassium dextran (LPD) than in the lungs treated with vaporized perfluorocarbon (PFC) + LPD. (H&E; magnification, ×100)

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Brazilian consensus on non-cystic fibrosis bronchiectasis

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ABSTRACT

Bronchiectasis is a condition that has been increasingly diagnosed by chest HRCT. In the literature, bronchiectasis is divided into bronchiectasis secondary to cystic fibrosis and bronchiectasis not associated with cystic fibrosis, which is termed non-cystic fibrosis bronchiectasis. Many causes can lead to the development of bronchiectasis, and patients usually have chronic airway symptoms, recurrent infections, and CT abnormalities consistent with the condition. The first international guideline on the diagnosis and treatment of non-cystic fibrosis bronchiectasis was published in 2010. In Brazil, this is the first review document aimed at systematizing the knowledge that has been accumulated on the subject to date. Because there is insufficient evidence on which to base recommendations for various treatment topics, here the decision was made to prepare an expert consensus document. The Brazilian Thoracic Association Committee on Respiratory Infections summoned 10 pulmonologists with expertise in bronchiectasis in Brazil to conduct a critical assessment of the available scientific evidence and international guidelines, as well as to identify aspects that are relevant to the understanding of the heterogeneity of bronchiectasis and to its diagnostic and therapeutic management. Five broad topics were established (pathophysiology, diagnosis, monitoring of stable patients, treatment of stable patients, and management of exacerbations). After this subdivision, the topics were distributed among the authors, who conducted a nonsystematic review of the literature, giving priority to major publications in the specific areas, including original articles, review articles, and systematic reviews. The authors reviewed and commented on all topics, producing a single final document that was approved by consensus.

Keywords: Bronchiectasis; Tomography, X-ray; Radiography, thoracic.

INTRODUCTION

Socioeconomic impact of bronchiectasis

Once considered an orphan disease,[1] permanent airway dilatation, known as bronchiectasis, is a condition that is more common than previously thought. The widespread use of chest HRCT is probably the major factor in the increased diagnosis of bronchiectasis, since it contributes greatly to the detection and better visualization of dilated bronchi and other bronchial and bronchiolar abnormalities. Other important factors in the increased diagnosis of bronchiectasis are the aging of the population, the increased rates of other pathological conditions that can be associated with the development of bronchiectasis, and more widespread diagnostic suspicion.

Data from the Brazilian National Ministry of Health show that, in Brazil, the rate of hospitalization for chronic respiratory diseases decreased from 434.4/100,000 population in 2003 to 241.8/100,000 population in 2013. Of the latter total, 54.5% were due to obstructive diseases and only 0.37% (0.9/100,000 population) were due to bronchiectasis. As regards the mortality rate in 2013, although obstructive diseases accounted for 64% of all deaths from chronic respiratory diseases (33.6/100,000 population), bronchiectasis resulted in a mortality rate of 0.2/100,000 population.[2] It should be emphasized here that these national data may be underestimated because they are based exclusively on hospital inpatient information.

Global epidemiological data shows that the diagnosis of bronchiectasis has increased, with disease prevalence increasing with age and varying geographically

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and ethnically.[3] In the USA, an annual increase of 8.7% has been reported for the 2000-2007 period,[4] as has a similar increase among women and the elderly between 2009 and 2013.[5] In the United Kingdom, the incidence and prevalence rates of bronchiectasis have increased annually since 2004 and are associated with significant mortality.[6] Recent estimates indicate a prevalence rate of 1 in every 206 men and 1 in every 176 women in the United Kingdom; 1 in every 276 people in Spain; and 1 in every 1,492 people in Germany.[6-8] These numbers may be underestimated if we consider the fact that COPD patients can present with bronchiectasis on HRCT at rates ranging from 29-50% in different publications.[9-11]

The socioeconomic impact of bronchiectasis has been more fully studied in recent years. In the USA, a pharmacoeconomic study based on a large database showed that the average increase in overall health costs after the first year of diagnosis of bronchiectasis, compared with controls, was US$2,319.00.[12]

Treatment costs increase with disease severity and with factors such as age, chronic *Pseudomonas aeruginosa* infection, exacerbations, and hospital admissions.[13] In a study conducted in Spain, the mean annual cost per patient with bronchiectasis was €4,671.00, and this value doubled with each increase in severity (as determined by the FACED score[1]). In patients with mild disease, the costs were mainly due to the use of bronchodilators and inhaled corticosteroids, and, in those with severe disease, they were mainly due to exacerbations and the use of inhaled antibiotics.[13] The therapeutic management of some subgroups of patients, such as individuals with COPD, also consumes more financial resources.

These findings underscore the importance of diagnosis and appropriate management of bronchiectasis patients. In addition, preventing exacerbations should be a goal not only to improve quality of life and preserve lung function but also to reduce the economic costs associated with bronchiectasis.[14,15]

Referral centers/multidisciplinary care

In Brazil, a survey conducted by the Committee on Respiratory Infections and Pulmonary Mycoses of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) showed that, in 2012, most bronchiectasis patients were treated in general outpatient clinics (66%). Only 22% were treated in specialized bronchiectasis outpatient clinics, and the remaining 12% were treated in integrated outpatient clinics combining pulmonology and cystic fibrosis care (Figure 1; unpublished data).

Given the complexity of the etiologic diagnosis of bronchiectasis and the multisystem nature of this condition, there is a need for multidisciplinary management, preferably performed in centers with experience in the care of bronchiectasis patients. The improvement in the survival of cystic fibrosis patients is one example of the benefits of this type of approach. In addition to early diagnosis and access to medications, multidisciplinary care at a referral center is a determinant of disease course in cystic fibrosis patients.[16]

A referral center for non-cystic fibrosis bronchiectasis should have resources to carry out a careful etiologic investigation that will enable the establishment of the correct diagnosis, as well as expertise for the pharmacological and non-pharmacological management of various levels of severity. The multidisciplinary team should include physicians (pulmonologists and chest surgeons), nurses, physical therapy professionals, pharmacists, nutritionists, and social workers. In addition, it should be associated with qualified pulmonary function and microbiology laboratories and have access to pulmonary rehabilitation programs.[17,18]

METHODOLOGY

The SBPT Committee on Respiratory Infections summoned 10 pulmonologists with expertise in bronchiectasis in Brazil to conduct a critical assessment of the available scientific evidence and international guidelines, as well as to identify aspects that are relevant to the understanding of the heterogeneity of the clinical presentation of bronchiectasis and its diagnostic and therapeutic management. Five broad topics were established (pathophysiology, diagnosis, monitoring of stable patients, treatment of stable patients, and management of exacerbations). After this subdivision, the topics were distributed among the authors, who conducted a nonsystematic review of the literature, giving priority to major publications in the specific areas, including original articles, review articles, and systematic reviews. All authors had the opportunity to review and comment on all topics, producing a single final document that was approved by consensus.

DEFINITION AND PATHOPHYSIOLOGY

The term bronchiectasis refers to evidence of irreversible bronchial dilatation, usually found on chest CT scans. There are many congenital and acquired conditions related to the onset of bronchiectasis (Chart 1).[19] The most widely accepted hypothesis to explain the onset of bronchiectasis is the one that proposes an interaction, at different levels of intensity, between an environmental insult and an individual with congenitally susceptible lungs. Increased susceptibility is an impairment of pulmonary defense mechanisms, such as mucociliary transport and availability of IgG and antiproteases in the distal air spaces.[20]

Impaired defense mechanisms make the elimination of inhaled biological and non-biological particles and toxic gases less efficient. These agents remain in both the proximal and distal airways. Retained bacteria and viruses proliferate within the airways, change the composition of the normal lung microbiome, and

1 FACED: acronym for **F**EV$_1$, **A**ge, **C**hronic colonization with *Pseudomonas aeruginosa*, **E**xtent (of CT findings), and **D**yspnea.

trigger inflammation. Prolonged inflammation causes pulmonary structural damage and further impairs the mechanisms of airway clearance. Thus, the well-known vicious cycle implicated in the pathophysiology of bronchiectasis is initiated (Figure 1).[20]

A characteristic common to several conditions associated with the onset of bronchiectasis is the concomitant lesion of the small and large airways. This has been demonstrated in chronic bronchitis of COPD and in cystic fibrosis.[21,22] Nonspecific inflammatory processes of the small airways (bronchiolitis and bronchiolectasis) may even precede disease onset.

The condition that triggers the vicious cycle described above cannot always be identified. In such cases, patients have a presumptive diagnosis of idiopathic bronchiectasis. Although pulmonary involvement in bronchiectasis is usually diffuse and bilateral, in rare cases, bronchial obstruction may lead to localized bronchial dilatation because it prevents the proper functioning of mucociliary transport.

Chief among the conditions that affect the lungs diffusely are some viral infections (adenovirus; measles)[23-25] and bacterial infections (pertussis; bacterial pneumonias),[26] all of which can act as triggers for the development of bronchiectasis. In Brazil, pulmonary tuberculosis is also of note because it is a disease that has high incidence and prevalence[27] and leaves lung sequelae in the form of different size areas of chronic bronchial dilatation.[28]

Conditions that directly affect airway clearance, such as ciliary dyskinesia and cystic fibrosis, can also be triggers of events leading to diffuse bronchiectasis. Ciliary dyskinesia impairs the functioning of the ciliary apparatus and leads to accumulation of secretions, especially in the small airways.[29] Cystic fibrosis, whose genetic defect results in thicker, harder to clear secretions, shows a trend toward accumulation of these secretions in the small airways and an increased risk of bacterial contamination.[16,22]

The design of the airways, similar to a tree, in which new branches grow dichotomously, allows the identification of bronchial generations. From the trachea to approximately bronchial generation 6, air is transported by convection (pressure gradient) and there is airflow. As the cross-sectional area progressively increases with every new airway generation, the airflow progressively decreases until, at around bronchial generation 15, there is no airflow and the gas molecules move by diffusion.[30] From this

Chart 1. Causes and conditions associated with bronchiectasis.

Congenital conditions	Cystic fibrosis[a]	
	Alpha-1 antitrypsin deficiency[a]	
	Primary ciliary dyskinesia[a]	
	Young's syndrome	
	Primary ((humoral, cellular, or combined) immunodeficiencies[a]	
	Anatomical defects in the tracheobronchial tree (tracheobronchomalacia [Williams-Campbell syndrome], tracheobronchomegaly [Mounier-Kuhn syndrome])	
	Pulmonary sequestration	
Acquired conditions	Post-infectious	Tuberculosis, nontuberculous mycobacterial infections
		Fungal infections (e.g., *Paracoccidioides brasiliensis*)
		Viral infections (adenovirus, measles virus)
		Swyer-James-MacLeod's syndrome
		Bacterial diseases (*Staphylococcus aureus*, other bacteria)
	Chronic obstructive respiratory diseases	COPD, bronchial asthma
	Secondary immunodeficiencies	HIV, neoplasms, treatment with immunosuppressants or biological agents
	Systemic diseases (autoimmune mechanisms)	Rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus
		Inflammatory bowel disease (Chron's disease, ulcerative colitis)
	Hypersensitivity-mediated	Allergic bronchopulmonary aspergillosis
	Secondary to inflammatory pneumonitis	Gastroesophageal reflux disease, chronic microaspiration, radiotherapy, inhalation of gases or other toxic agents
	Localized (obstructive) processes	Intrabronchial (benign tumors, foreign body aspiration)
		Extrabronchial (lymph node enlargement, tumors)
	Post-transplant (immune-mediated)	Host-versus-graft reaction (bone marrow transplantation, lung transplantation)
	Other (rare) conditions	Yellow nail syndrome, sarcoidosis, endometriosis, amyloidosis, diffuse panbronchiolitis
Idiopathic conditions (unknown cause)		

[a]Conditions known to be hereditary.

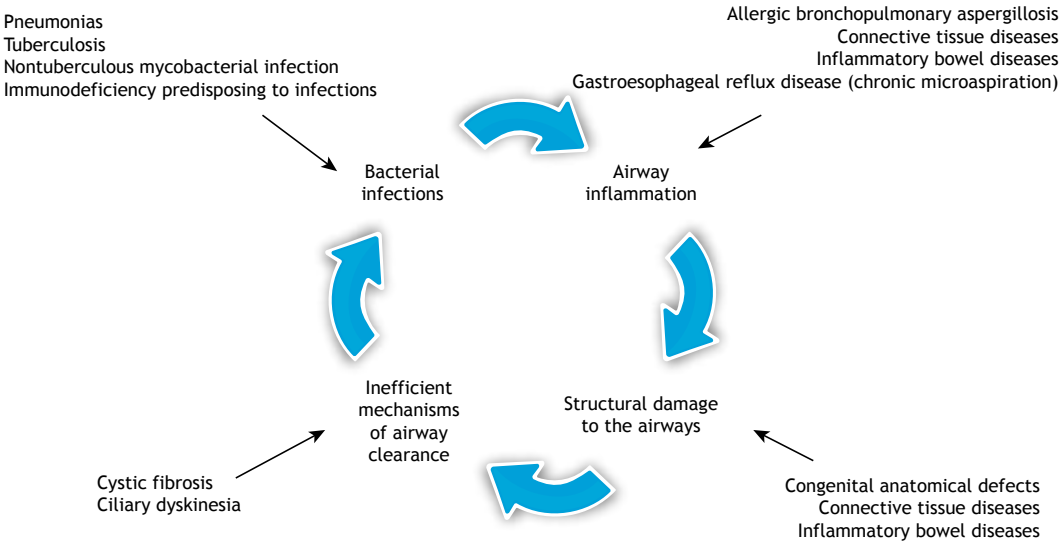

Figure 1. Pathophysiology of bronchiectasis: a "vicious cycle" of the various factors involved.

airway structure, we can conclude that cough, which is dependent on flow generation, replaces mucociliary transport completely only up to bronchial generation 6. From generation 7 onward, cough progressively loses its effectiveness, and cough cannot compensate for impaired mucociliary transport from generation 15 onward.[31,32]

In cases in which mucociliary transport is ineffective, all inhaled contaminants tend to settle out in the small diameter airways. The incoming bacteria find an environment that is highly conducive to proliferation in that region. The retained chemical and biological agents trigger an inflammatory response that causes more structural damage and further impairs mucociliary transport.

A groundbreaking study by Reid[33] showed, by correlating bronchogram findings and pathology study of surgically resected lobes, that the involvement of large and small airways is often concomitant in bronchiectasis patients. In addition to the lesions in large airways, the author observed small airways whose lumens were partially or totally obstructed by inflammation and/or fibrosis. In many cases, the bronchioles disappeared from their normal position near the pulmonary arteriole and only remains of their structure were found. Depending on the severity of the bronchiolar obliteration, the bronchogram findings included cylindrical bronchiectasis (the least common bronchiolar obliteration), varicose bronchiectasis (the most common obliteration), or cystic/saccular bronchiectasis, in which all small diameter airways were obliterated. This loss of small airways resulted in a much smaller number of bronchial generations being identified. Bronchiectasis therefore appears to be a pattern of bronchial response to various types of injury, which as a rule involve (predominantly neutrophilic) inflammation and in most cases involve chronic airway infections.

DIAGNOSIS

Diagnosis of bronchiectasis is defined by the presence of (non-reversible) bronchial dilatations on HRCT, which means that this is the imaging modality required and sufficient to confirm or rule out the diagnosis. The causes and associated conditions should then be investigated (Chart 1).

Radiological aspects

Since its introduction in the 1980s, HRCT has become the gold standard for the diagnosis and evaluation of the extent of airway structural changes. HRCT allows the identification of changes in large diameter airways, such as luminal dilatation and wall thickening. In general, changes in the small airways are also detected and can be described as direct and indirect signs; in some cases, these signs can be eventually seen with no dilatation in central bronchi. Direct signs are the visualization of bronchioles that may be dilated (bronchiolectasis), with their lumen filled with secretion (small, low-density nodules; tree-in-bud pattern) or with thick walls. The tree-in-bud pattern is the visualization of millimetric airway branching, invisible in normal situations, and made possible to be seen by the accumulation of secretion, inflammatory changes, and airway dilatation.[34]

The presence of mosaic attenuation, more easily identifiable on TC scan slices obtained during exhalation, is the so-called "indirect sign", which is due to trapping of air in the lobules as a result of subocclusion of the bronchiolar lumen due to bronchiolar wall inflammation/fibrosis.[35] Signs of collapse of lung regions because of recurrent infections may also be seen in some cases. Some of the changes described above can be observed in Figures 2, 3, and 4.

Additional HRCT findings can suggest a specific cause. For example, presence of concomitant emphysema

is suggestive of COPD, evidence of *situs inversus* or profusion of nodules suggestive of bronchiolar mucoid impaction in the lower lung fields should lead to ciliary dyskinesia, and evidence of tracheomegaly or pseudodiverticula in the tracheobronchial walls should bring to mind the Mounier-Kuhn syndrome.

The regional distribution of bronchiectasis can provide useful information for the etiologic diagnosis,[36] especially if the bronchiectasis is upper-lobe predominant, a common finding in cystic fibrosis. Predominant involvement of anterior regions (middle lobe and lingula) should lead to nontuberculous mycobacteria[37] or diffuse panbronchiolitis, the latter being classically described in Asians[38] and being rare in Brazil. Predominant involvement of lower lung fields is common to several conditions, such as ciliary dyskinesia[29]; conditions associated with chronic aspiration (a cause that should be remembered in patients with an altered mental status); swallowing impairment or gastroesophageal reflux disease[39]; bronchiectasis secondary to hypogammaglobulinemia; immunosuppression; and chronic rejection in (lung, bone marrow) transplant recipients. Central predominance with large mucoid impactions (finger-in-glove sign) is suggestive of allergic bronchopulmonary aspergillosis. In cases of bronchiectasis after pulmonary tuberculosis, the distribution of bronchiectasis is often asymmetric, with preferential involvement of upper lobes or apical segments of lower lobes; in addition, pleural thickening and adjacent parenchymal distortion are common. Localized bronchiectasis can be caused by bronchial obstruction, and, in such cases, bronchoscopic investigation is indicated.

Etiologic investigation

Evidence of bronchiectasis on HRCT is usually obtained during the evaluation of patients with a productive cough and/or recurrent respiratory infections of the upper and lower airways, and may be accompanied or not by chest X-ray abnormalities. For such patients, etiologic investigation after confirmation of the diagnosis by HRCT scan is recommended (Figure 5).

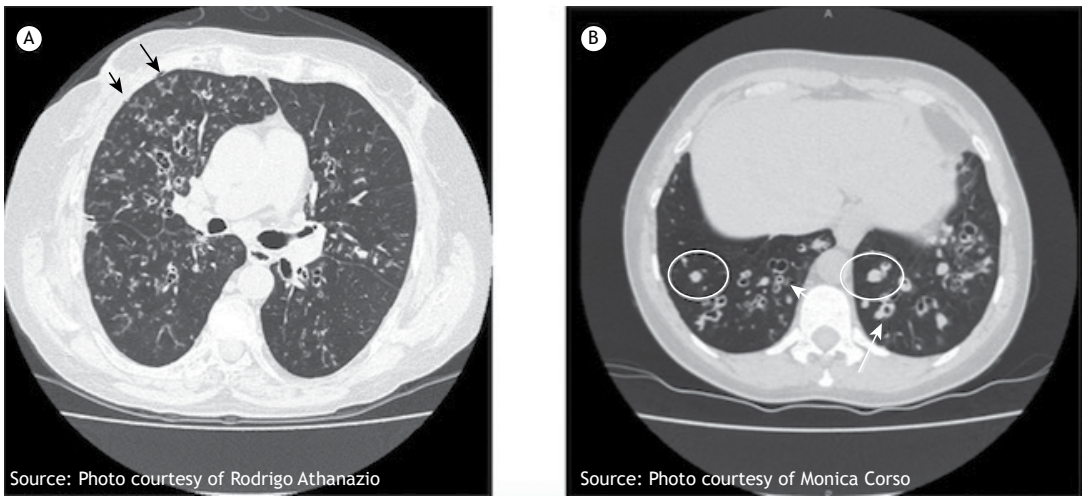

Figure 2. Chest HRCT scan. In A, tree-in-bud pattern (arrows). In B, mucoid impaction (mucus plug) in small airways (circles) and bronchial wall thickening (arrows).

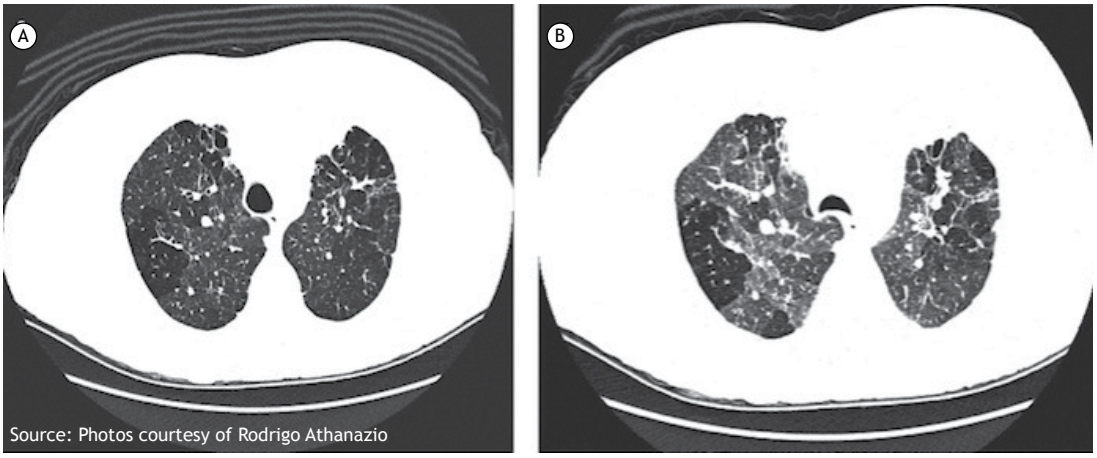

Figure 3. Chest HRCT scan. Mosaic perfusion (or attenuation). Although present in A (inhalation), it is more visible in B (exhalation). The darker areas indicate air trapping due to small airways impairment, associated with oligemia.

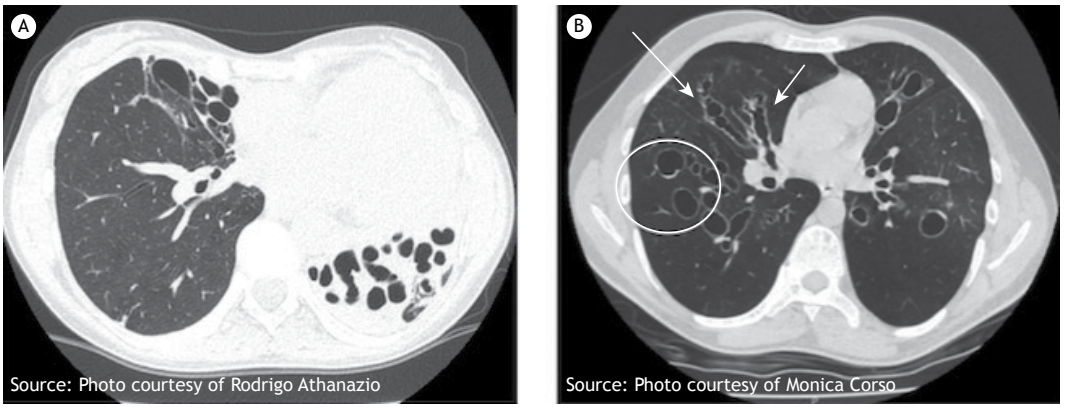

Figure 4. Chest HRCT scan. In A, cystic bronchiectasis in fibroatelectatic areas. In B, varicose bronchiectasis (arrows) and cystic bronchiectasis (circle). Note the loss of bronchial generations (loss of millimetric branching) and impaired visualization of bronchovascular markings, suggestive of air trapping (even during inhalation).

Bronchiectasis may also be detected in patients with respiratory symptoms and with diseases/conditions that occasionally present with airway involvement (COPD, asthma, collagen diseases, inflammatory bowel diseases, cystic fibrosis, and gastroesophageal reflux disease). Even when the cause is known, the possibility of concomitant conditions should be remembered; for example, asthma associated with gastroesophageal reflux disease or allergic bronchopulmonary aspergillosis, and collagen disease associated with infections, such as mycobacterial infection.

The major causes of and major conditions associated with bronchiectasis are listed in Chart 1. In published series, the frequency of each of them may vary according to the region studied (higher prevalence of infections) and the availability of ancillary tests that are necessary for the diagnostic investigation. In most series, post-infectious etiologies are some of the most common, accounting for 20% to 32% of cases.[40-42] Bronchiectasis should be considered to be of "unknown cause" (24-40% of cases)[40,41] only in patients in whom a diagnosis cannot be established even after all recommended tests are performed. In a study[41] that analyzed 1,258 patients from seven databases (Italy, the United Kingdom, Belgium, Spain, Greece, and Ireland), the cause of bronchiectasis was not established in 40%, was post-infective in 20%, was COPD-related in 15%, was connective tissue disease-related in 15%, was immunodeficiency-related in 5.8%, and was asthma-related in 3.3%.

In the study validating the FACED score, conducted in six centers in Latin America (four of which in Brazil), among the 651 patients enrolled, the cause of bronchiectasis was classified as post-infective in 40.3%; idiopathic in 31.1%; ciliary dyskinesia-related in 9.0%; airway disease-related (COPD, asthma, or bronchiolitis) in 5.1%; and rheumatic disease-related in 4.3%.[43]

The relevance of etiologic investigation lies in the fact that some conditions may benefit from specific therapeutic measures (allergic bronchopulmonary aspergillosis, collagen diseases, immunodeficiencies, aspiration, ciliary dyskinesia, cystic fibrosis, bronchial obstruction, COPD, and asthma), and this may occur in 13%[41] to 37%[42] of cases.

FOLLOW-UP AND MONITORING

Functional aspects

All bronchiectasis patients should undergo periodic functional assessment to detect any sign of decreased pulmonary function as early as possible. To that end, spirometry with bronchodilator use is satisfactory in the vast majority of cases. Obstructive lung disease is the most common finding, but significant reductions in FVC can be found in more advanced disease, with increased lung parenchymal destruction. End-expiratory flows are reduced, the RV/TLC ratio is increased (suggesting air trapping), and FVC and TLC are normal or low.[44,45] Decreased FEV_1 correlates with the presence of dyspnea—as assessed by the modified Medical Research Council (mMRC) scale—and with the extent of disease on HRCT.[46] Approximately 33% of bronchiectasis patients have positive methacholine or histamine challenge test results. DLCO test results are usually normal; DLCO may be reduced in advanced disease and in the presence of associated emphysema.[47]

The six-minute walk test and the incremental shuttle walk test can provide additional functional information to spirometry.[48,49] The first has the advantage of having been extensively validated in respiratory diseases, and basically requires space and trained personnel in order to be performed.[50] In this context, the six-minute walk distance correlates better with quality of life than with functional tests.[51] The shuttle test can be useful especially in patients with preserved pulmonary function, because of the potential "ceiling effect" of the six-minute walk test, and has been validated for bronchiectasis patients.[49,52]

Our recommendation:

Perform spirometry with bronchodilator use every 6 months, lung volume assessment (if available) annually, and the six-minute walk test (at the physician's discretion).

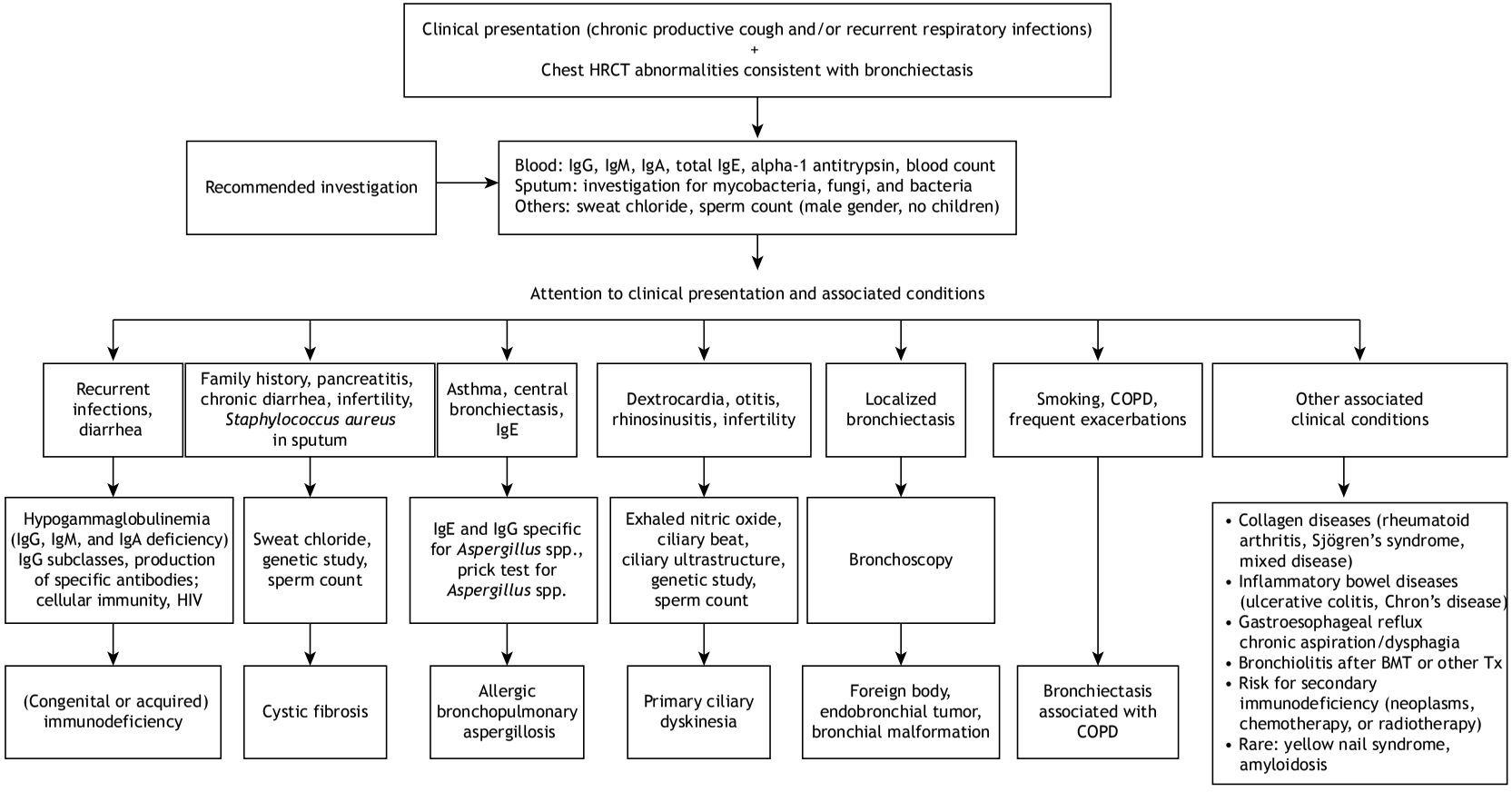

Figure 5. Algorithm for the diagnosis and etiologic investigation of bronchiectasis. BMT: bone marrow transplantation; and Tx: transplantation.

Microbiological aspects

The identification of potentially pathogenic microorganisms (PPMs) in the airways of bronchiectasis patients is a common finding related to increased bronchial inflammation and, consequently, progressive clinical deterioration.[53] Colonization is understood as the presence, growth, and multiplication of a microorganism in a host without there being any clinical expression or detection of immune response.[54] In this context, the term "bronchial colonization" should be avoided, because the presence of PPMs in the lower airways is not innocuous, and it would therefore be more appropriate to use the term "chronic bronchial infection". There is strong evidence that PPMs are associated with an accelerated decline in pulmonary function, a higher number of exacerbations, worsening of quality of life, and higher mortality.[17,53,55,56]

PPMs are understood as various species of gram-negative and gram-positive bacteria, mycobacteria, and fungi that have the ability to directly cause lung injury. Recent studies assessing the microbiome have revealed the existence of a great abundance and variety of bacteria in the lower respiratory tract, a finding that is one of the determinants of proper lung functioning and protection against recurrent infections. In bronchiectasis patients, this variety of bacteria is reduced as the proportion of a potentially pathogenic species increases with the severity of the disease. Given the loss of bronchial architecture and the impairment of local defense mechanisms in such patients, there is a greater risk that a PPM will chronically infect their respiratory tract. Chronic bronchial infection may produce changes in the balance of the lung microbiota, and this has a negative impact on the clinical course of the disease.[57,58] The association of a PPM with the sharp decline caused by the disease is well documented in patients with chronic bronchial infection with *P. aeruginosa*.[59] The presence of other bacteria may also cause an accelerated clinical deterioration; however, the real impact of such infections has yet to be fully determined.[60] For example, a recent study using a large American database showed that the identification of methicillin-sensitive *Staphylococcus aureus* does not appear to be an independent risk factor for severe disease in bronchiectasis patients.[61]

Some definitions should be highlighted in this context:

- Primary infection: when a first positive culture for a PPM that was not isolated in previous periodic tests is obtained
- Intermittent bronchial infection: when culture results for a specific PPM are sometimes positive and sometimes negative in samples collected at intervals of at least 1 month after a primary infection
- Chronic bronchial infection: when two or more cultures are positive for the same PPM over a 12-month period in samples collected at intervals of at least 3 months
- Eradication: when a specific PPM is no longer detected in at least two consecutive samples collected at an interval of at least 1 month over a 6-month period

Sputum is the specimen of choice for culture in order to identify PPMs in bronchiectasis patients. Sputum samples should be immediately delivered to the laboratory or kept under refrigeration for as long as 3 h after collection.[62] In addition, sputum should be microscopically evaluated to ensure the quality of the sample obtained and its representativeness in terms of the lower respiratory tract, it being necessary that more than 25 leukocytes and less than 10 epithelial cells should be identified per field at a magnification of ×100. In patients who have difficulty expectorating, samples obtained by BAL may be necessary. In such cases, the samples must be quantitatively cultured.[63] When a PPM is identified, antibiotic susceptibility testing is recommended for guiding the choice of systemic antibiotic therapy. However, there is increasing evidence of poor correlation between in vitro susceptibility and in vivo clinical response, especially in the case of biofilm-producing bacteria.[64] Therefore, clinical judgment should guide therapeutic decisions. It is important to emphasize that susceptibility testing is not appropriate for the choice of an inhaled antibiotic. When the inhalation route is used, the drugs reach high concentrations in the lower respiratory tract and their clinical efficacy may remain even in situations of bacterial resistance demonstrated in vitro.[65]

Our recommendation:

Collect samples from the lower respiratory tract (sputum, for example) at regular intervals of 3-4 months and during pulmonary exacerbations for aerobic culture, as well as annually for culture for fungi and mycobacteria. If the patient is being treated with chronic macrolide therapy, culture for mycobacteria should be performed every 6 months.

Quality of life

Some studies have revealed that bronchiectasis patients have reduced quality of life, fatigue symptoms, and asthenia, as well as high scores on depression and anxiety measures.[66,67]

Higher levels of depression are associated with greater severity of dyspnea.[68] Patients with chronic bronchial infection with *P. aeruginosa* have poorer quality of life than those with chronic infections with other bacteria.[66] In addition, chronic cough has a negative impact on the quality of life of such patients and their families.[69] However, one group of authors demonstrated that disease severity as measured by CT does not correlate with psychological well-being.[67]

Systemic markers

Inflammatory markers, such as C-reactive protein (CRP) and total leukocyte counts, are related to the extent of disease and to poorer pulmonary function.[70] One study demonstrated that, in stable patients, increased bronchiectasis severity, as assessed by the Bronchiectasis Severity Index (BSI) and the FACED score, correlated with higher CRP levels but not

with total leukocyte counts or with the neutrophil/lymphocyte ratio.[71]

Airway inflammation has a predominance of neutrophils, which means that some inflammatory cytokines, such as IL-1, IL-6, and TNF-α, are increased, but IL-10 is decreased.[72] However, these cytokines are not markers used in clinical practice.

Our recommendation:

Although CRP appears to be an inflammation-related marker and is available for use in clinical practice, there is insufficient evidence to recommend its routine use to assess disease severity.

Severity and prognostic scores

Although there is a clear relationship of increased disease severity and mortality in bronchiectasis patients to chronic *P. aeruginosa* infection,[73] other factors contribute to the clinical and functional course of such patients. Since this is a difficult-to-manage condition, associated with various causes and great clinical heterogeneity, multidimensional scores have been developed in order to better estimate severity and prognosis. The most commonly used are the FACED score[74] and the BSI.[59]

The FACED score uses the following variables: FEV_1 (% predicted); age; chronic colonization with *P. aeruginosa*; extent of findings on chest HRCT (number of affected lobes; the lingula is counted as a separate lobe); and dyspnea, as assessed by the mMRC scale.[74] The E-FACED score added severe exacerbation in the previous year to the other variables of the FACED score and was found to be able to predict not only mortality but also the risk of exacerbation.[75] The FACED and the E-FACED scores are user-friendly and have been validated in patients in Brazil (Chart 2).[43] In addition to being useful to predict all-cause mortality and exacerbations, they showed excellent ability to discriminate between different levels of disease severity (from mild to severe). These scores can also be used in order to aid in the assessment of therapeutic response to the adopted interventions.[76]

The BSI includes, in addition to the variables of the FACED score, body mass index, chronic infection with microorganisms other than *P. aeruginosa*, hospitalizations, and exacerbations in the previous year. Although completing the BSI is a little more laborious, there is a homepage to that end on the Internet (http://www.bronchiectasisseverity.com/15-2/). The BSI also has good ability to estimate future mortality and exacerbations.[59]

Our recommendation:

A severity score and a prognostic estimate should be calculated at the time patients are diagnosed with bronchiectasis. Periodic calculation of the score (annually, for example) aids in therapeutic management. To date, the FACED and the E-FACED scores are the ones that have been validated for use in Brazil.

THERAPEUTIC MANAGEMENT OF STABLE PATIENTS

Despite the lack of medications approved by regulatory agencies for the treatment of bronchiectasis patients, various drugs and strategies have shown benefits in improving both quality of life and clinical outcomes. Since bronchiectasis is a complex and heterogeneous disease, treatment should be individualized, considering the peculiarities and clinical manifestations of each patient, and some specific conditions should be treated concurrently. However, some recommendations are important for all bronchiectasis patients, as are some interventions targeted at phenotypes specific to the disease (Figure 6).

Treatment of specific causes or conditions

Some causes of bronchiectasis have specific treatment or specific therapeutic measures. The detailing of those topics is beyond the scope of the present consensus statement, and there are excellent reviews and some guidelines that may be useful for expanding the knowledge on the topics (Chart 3).[16,29,77-84]

Chronic airway infection

Primary infection

There is consensus among experts on the need to attempt eradication in cases of primary *P. aeruginosa* infection.[15,85] Unlike cystic fibrosis, for which *P. aeruginosa* eradication protocols have been adequately established in various clinical trials,[86] evidence is scarce for non-cystic fibrosis bronchiectasis. In the context of cystic fibrosis, *P. aeruginosa* eradication protocols have been simplified to the use of 28-day regimens of inhaled antibiotics alone, with the same rate of efficacy.[87] However, most of those interventions occur in the pediatric age group, in patients whose lung architecture is still preserved. In contrast, non-cystic fibrosis bronchiectasis patients commonly present with extensive diffuse pulmonary involvement at the time the primary *P. aeruginosa* infection is identified. We suggest a 14- to 21-day regimen of systemic antibiotic therapy in conjunction with a longer than 3-month course of inhaled antibiotic therapy.[15,85,88] If the patient is infected with a quinolone-sensitive *P. aeruginosa* strain, we suggest that treatment be started with ciprofloxacin per oral; however, intravenous regimens can be used, such as an antipseudomonal beta-lactam combined with an aminoglycoside. If inhaled antibiotics are unavailable, treatment should consist only of systemic antibiotics. We recommend that follow-up sputum culture be performed 2-4 weeks after treatment completion. If the patient remains culture positive, another protocol can be attempted until a total of three attempts at eradication are made. Thereafter, the patient should be regarded as having chronic bronchial infection. Although the rate of eradication is lower in patients in whom the presence of *P. aeruginosa* mucoid strains is detected,

Chart 2. E-FACED score: acronym for **E**xacerbation, **F**EV_1, **A**ge, **C**hronic colonization with *Pseudomonas aeruginosa*, **E**xtent (of CT findings), and **D**yspnea.

Variables	Result	Score
Exacerbation	No	Zero
	Yes	2
FEV_1, % predicted	≥ 50%	Zero
	< 50%	2
Age	< 70 years	Zero
	≥ 70 years	2
Chronic colonization with *P. aeruginosa*	No	Zero
	Yes	1
Extent of CT findings: number of affected lobes	1-2 lobes	Zero
	> 2 lobes	1
Dyspnea, mMRC scale	0-II	Zero
	III-IV	1
		TOTAL: 0-9 points
Severity: 0-3 points: mild; 4-6 points: moderate; and 7-9 points: severe.		

mMRC: modified Medical Research Council.

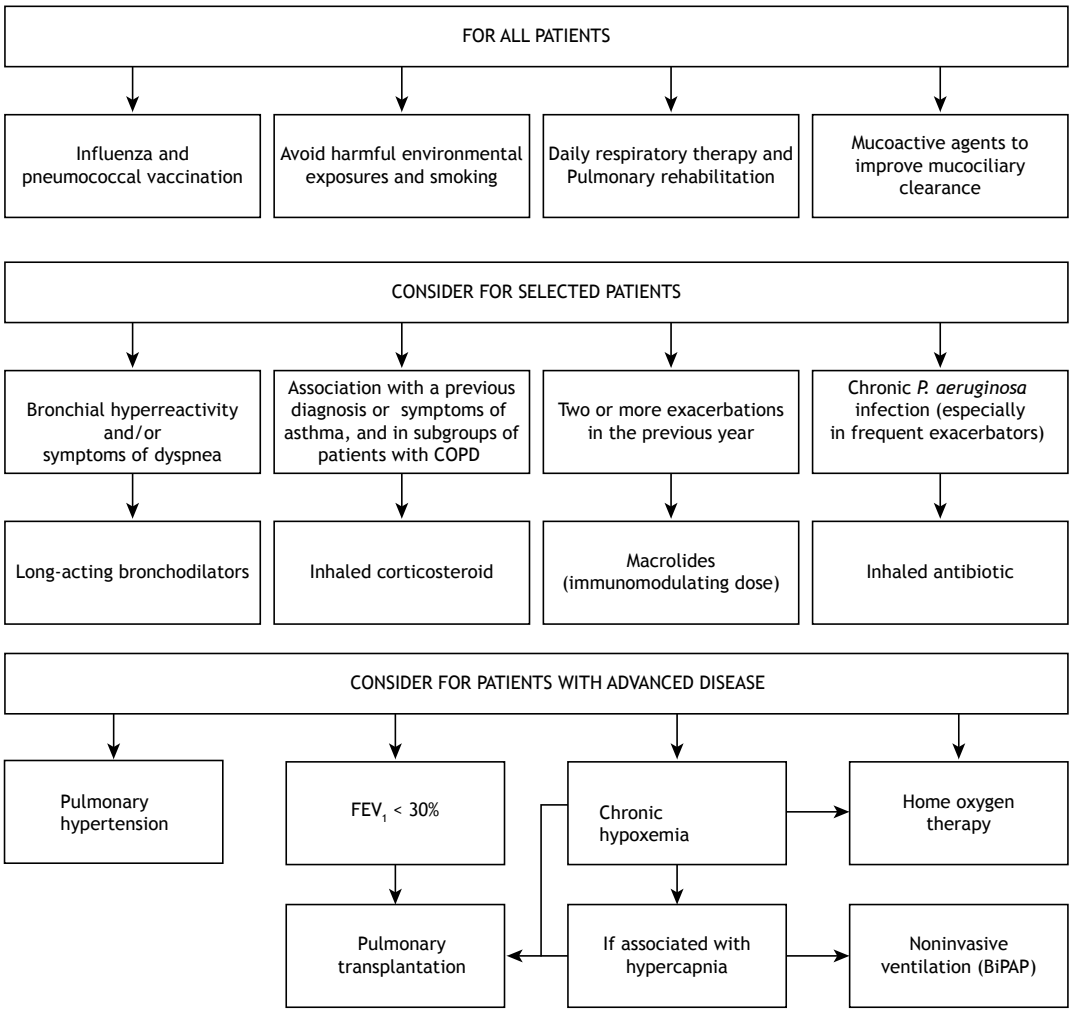

Figure 6. Algorithm for the therapeutic management of stable bronchiectasis patients. BiPAP: bilevel positive airway pressure.

this should not be a criterion for depriving patients of attempts at eradication.[89] Chart 4 presents the main treatment regimens recommended for the treatment of primary *P. aeruginosa* infection.

Chart 3. Causes of bronchiectasis that have specific treatment.

Condition or cause	Specific therapeutic measures
Allergic bronchopulmonary aspergillosis	Systemic corticosteroids, antifungal agents
Ciliary dyskinesia	Auditory monitoring, cardiac evaluation (malformations), guidance regarding difficulty in conceiving, mucociliary clearance techniques
Associated diseases (asthma, COPD, collagen diseases, inflammatory bowel disease, etc.)	Treatment of the underlying disease
Alpha-1 antitrypsin deficiency	Avoid tobacco exposure; consider replacement therapy in specific situations
Cystic fibrosis	DNase; consider CFTR modulators (if available and in the appropriate situation)
Immunodeficiencies	Periodic immunoglobulin replacement (i.v. or s.c.)
Nontuberculous mycobacterial infection	Treatment according to species and in accordance with national and international guidelines
Bronchial obstruction	Bronchoscopic clearance or surgical treatment
Gastroesophageal reflux disease	Inhibitor of acid gastric secretion; consider surgery

CFTR: cystic fibrosis transmembrane conductance regulator.

With regard to other PPMs, despite their potential deleterious effect on the clinical course of bronchiectasis patients, there is insufficient evidence to justify the adoption of eradication protocols in this context. However, in selected cases, characterized by progressive functional decline and/or severe exacerbation related to the first identification of a PPM, such as methicillin-resistant *S. aureus*, *Burkholderia cepacia*, *Achromobacter xylosoxidans*, or *Stenotrophomonas maltophilia*, an attempt at eradication should be made.

Our recommendation:

Immediately following the first identification of *P. aeruginosa* in the sputum of a patient, the patient should be treated with a systemic antipseudomonal antibiotic combined with an inhaled antibiotic. Follow-up sputum culture is recommended 2-4 weeks after treatment completion.

Chronic bronchial infection

In bronchiectasis patients with chronic *P. aeruginosa* infection, antibiotic use is associated with a decrease in sputum bacterial density, improved symptoms, and improved quality of life, as well as with a potential effect in reducing the number of pulmonary exacerbations.[90] Various antibiotic classes and formulations tested have demonstrated clinical benefits, especially in patients who are prone to exacerbations.[91] However, recent randomized clinical trials have shown conflicting results regarding the efficacy of the inhalation route.[92-94]

In Brazil, tobramycin and colistimethate are approved by the Brazilian National Health Oversight Agency for the treatment of cystic fibrosis and are marketed in the country; other classes of inhaled antibiotics, such as aztreonam and ciprofloxacin (both as a dry powder formulation and as nebulization of liposomes), are not available. Chart 5 shows the drugs and regimens recommended for the treatment of chronic bronchial infection with *P. aeruginosa* that are available in Brazil. These medications are approved and marketed in the country. Despite their availability in the country, these medications have a high price and are therefore usually obtained through public, high-cost medication dispensation protocols, which currently exist only for patients with bronchiectasis associated with cystic fibrosis. There is no evidence of superiority of one option over the other.

With regard to inhaled gentamicin, it is of note that, in the main clinical trial that tested it (compared with placebo), it was used as long-term therapy.[95] Alternate month use is based on the experience with the use of inhaled antibiotics in cystic fibrosis and is justified because it reduces the emergence of resistant strains.

Bronchospasm is a common adverse effect that can be minimized by using a bronchodilator prior to using an inhaled antibiotic. Hemoptysis as an adverse effect is not uncommon. Whenever possible, formulations developed and tested for inhalation should be preferred to intravenous formulations because of the reduced risk of adverse events.

In patients with chronic infection with PPMs other than *P. aeruginosa*, the lack of evidence does not allow us to recommend the use of inhaled antibiotic therapy. Chronic use of systemic antibiotics (orally or as intravenous cycles) should not be routinely recommended in bronchiectasis patients because of the lack of evidence and the risks associated with repeated exposure to these medications. However, selected cases in which the number of exacerbations remains high and quality of life remains poor, despite optimal treatment, may benefit from this strategy.[96]

Our recommendation:

Bronchiectasis patients with chronic *P. aeruginosa* infection and exacerbations may benefit from and should be treated with long-term inhaled antibiotics. The choice will depend on the availability of and access to medication.

Chart 4. Main treatment regimens recommended for the treatment of primary *Pseudomonas aeruginosa* infection in bronchiectasis patients.

Treatment regimen	Dose	Frequency
Oral antibiotic + inhaled antibiotic		
Oral:		
Ciprofloxacin	500-750 mg[a]	12/12 h for 14-21 days
+		
Inhaled:		
Gentamicin or	80 mg	12/12 h for 3 months
Nebulized tobramycin or	300 mg	12/12 h for 3 months
Colistimethate**	1,000,000 IU	12/12 h for 3 months
Intravenous antibiotic (antipseudomonal beta-lactam + aminoglycoside) + inhaled antibiotic		
Intravenous:		
Ceftazidime or	2 g	8/8 h (14 days)
Cefepime or	2 g	8/8 h (14 days)
Piperacillin + tazobactam or	4.5 g	6/6 h or 8/8 h (14 days)
Meropenem	2 g	8/8 h (14 days)
+		
Intravenous:		
Amikacin or	20-30 mg/kg/day (max 1.5 g/day)	24/24 h (14 days)
Gentamicin or	3-5 mg/kg/day (max 160 mg/day)	24/24 h (14 days)
Tobramycin	10 mg/kg/day (max 660 mg/day)	24/24 h (14 days)
+		
Inhaled:		
Gentamicin or	80 mg	12/12 h (3 months)
Nebulized tobramycin or	300 mg	12/12 h (3 months)
Colistimethate[b]	1,000,000 IU	12/12 h (3 months)

Max: maximum. [a]The dose of 750 mg, p.o., 12/12 h is indicated for patients weighing more than 50 kg. [b]If inhaled antibiotics are not available, consider treating the primary infection with systemic antibiotics alone.

Chart 5. Inhaled antibiotics available in Brazil[a] and recommended for the treatment of chronic bronchial infection with *Pseudomonas aeruginosa* in bronchiectasis patients.

Antibiotic and formulation	Dose	Frequency
Nebulized colistimethate	1,000,000 IU	12/12 h continuously
Gentamicin[b]	80 mg	12/12 h continuously (or in alternating cycles of 28 days)
Dry powder tobramycin	112 mg	12/12 h in alternating cycles of 28 days
Nebulized tobramycin	300 mg	12/12 h in alternating cycles of 28 days

[a]See details in the text regarding access to inhaled antibiotics. [b]Some centers dilute the intravenous formulation in 0.9% saline for nebulization; considerable caution should be exercised because of the risk of more side effects and bronchospasm.

Chronic inflammation

Macrolides

Macrolides are the only class of molecules with antibacterial and anti-inflammatory properties, although these immunomodulatory effects are not fully understood. Three large randomized clinical trials of long-term use of macrolides (azithromycin or erythromycin) showed a reduction in the frequency of exacerbations in adults with bronchiectasis who had had one to three exacerbations in the previous year: one involving 141 patients on either azithromycin or placebo for 6 months[97]; one with 83 patients treated with either azithromycin or placebo for 12 months[98]; and one with 117 patients treated with either erythromycin or placebo for 12 months.[99] A meta-analysis of nine studies (530 patients) demonstrated that macrolide use improved quality of life, reduced the number of patients with exacerbations, and reduced the number of exacerbations per patient.[100] A recent review pointed out that the evidence for the reduction in the frequency of exacerbations and improvement in quality of life is derived from studies of azithromycin, rather than other macrolides, predominantly in adults.[101] Among macrolides, azithromycin has the longest half-life and decreased cell efflux, which means that it reaches higher intracellular levels when administered long-term. The azithromycin doses used in clinical trials or in clinical practice are 500 mg/day or 250 mg/day three times a week, or 250 mg daily.

The most common adverse effect of macrolides is diarrhea, although treatment discontinuation due to diarrhea is rare.[100,102-105] With long-term use there is also the possibility of increased resistance of oropharyngeal commensal streptococci[98,99] and of emergence of nontuberculous mycobacteria.[15,106]

When prescribing macrolides, one should take into account the risk of electrocardiographic QT interval prolongation. Among macrolides, azithromycin poses the lowest risk of QT interval prolongation, whereas erythromycin poses the highest.[107] Cardiac risks

associated with macrolides are increased in the first 5 days of use.[108] A meta-analysis of bronchiectasis patients (comparing macrolides with placebo or usual medical care) found no association between macrolide use and an increased risk for adverse cardiac events,[100] but the data are limited and do not allow us to rule out cardiac risk in such patients.[101]

It is important that, before the medication is started, an electrocardiogram be performed and the patient's history of cardiac risk factors and use of potentially arrhythmogenic drugs be investigated.

The European Respiratory Society 2017 guidelines[15] recommend macrolides as first-line therapy for patients with no evidence of *P. aeruginosa* infection in order to reduce exacerbations. For individuals infected with this pathogen, macrolides are recommended as second-line therapy, with inhaled antibiotics being the first choice of treatment.[15]

Our recommendation:

Use macrolides as continuous therapy for at least 6-12 months for bronchiectasis patients with at least two exacerbations per year. Prefer azithromycin. The use of macrolides may be considered, although there is no evidence, for patients with fewer than two exacerbations per year but with a history of severe exacerbations or primary or secondary immunodeficiency, those whose exacerbations have a significant impact on their quality of life, and those with more severe bronchiectasis. Active nontuberculous mycobacterial infection should be ruled out.

Inhaled corticosteroids

Bronchiectasis patients have airway inflammation and, sometimes, symptoms similar to those of asthma or COPD. A recent review found only seven randomized placebo-controlled studies on the use of inhaled corticosteroids in bronchiectasis. All of those studies involved adults with stable disease, only one of which assessed long-term outcomes (over 6 months), and there was insufficient evidence to support the routine use of inhaled corticosteroids. There are no studies on the use of inhaled corticosteroids during exacerbations or in children, and there is not enough data on unwanted side effects.[109]

According to the aforementioned guidelines,[15] inhaled corticosteroids play no role in the routine management of bronchiectasis. Routine treatment with inhaled corticosteroids is recommended only if there is associated asthma or in the subgroup of patients with COPD and an indication for inhaled corticosteroid use.[15]

Our recommendation:

There is insufficient evidence to support the routine use of inhaled corticosteroids in adults with bronchiectasis. Inhaled corticosteroid therapy may be justified in some subgroups of adults if there is associated asthma or COPD.

Airflow obstruction

Bronchodilators

Most bronchiectasis patients have airflow obstruction,[110] but other spirometric patterns (reduced FVC, mixed patterns, or preserved pulmonary function) can also be observed.[15] There are few controlled studies that have assessed bronchodilator therapy in bronchiectasis. There is no evidence to support the routine use of bronchodilators in patients without dyspnea or respiratory symptoms, because there are no randomized controlled studies investigating the effectiveness of the use of short-acting[111] or long-acting[112] β_2 agonists. There is limited and indirect evidence for the benefit of long-term treatment with bronchodilators, evidence extracted from a study that compared a high-dose inhaled corticosteroid with a medium-dose long-acting β_2 agonist/inhaled corticosteroid combination.[113] In that study, combination therapy was advantageous, there being a decrease in dyspnea, better cough control, better quality of life, and a reduction in the use of rescue medication (β_2 agonists). However, the study did not report on improvement in pulmonary function, the types of pathogens isolated, or increased adverse effects.[113]

With regard to anticholinergics, there are no recent studies, and none of the few existing studies has met criteria for inclusion in systematic reviews, which means that there is no evidence to recommend the routine use of anticholinergics. The older drugs tend to dry secretions and reduce mucociliary transport, with potential deleterious effects.[114]

Guidelines on bronchiectasis recommend that long-acting bronchodilators be used only when bronchiectasis is associated with asthma or COPD,[15,47] since there is no evidence beyond that which exists for these conditions.[112,114] Spanish guidelines,[85] as well as those of the European Respiratory Society,[15] recommend the use of long-acting bronchodilators in symptomatic patients with airflow obstruction; the latter[15] recommend treatment discontinuation if there is reduction in symptoms, whereas the former[85] additionally recommend the use of short-acting bronchodilators prior to respiratory therapy and prior to the use of inhaled hypertonic solutions and/or inhaled antibiotics.

Our recommendation:

There is insufficient data to recommend the routine use of bronchodilators in bronchiectasis patients without dyspnea. Long-acting bronchodilators may be recommended if bronchiectasis is associated with asthma or COPD. Because of the potential risk of bronchospasm resulting from the use of inhaled mucoactive drugs and inhaled antibiotics, it is suggested that bronchodilators be used prior to using these drugs.

Airway clearance

In bronchiectasis, the changes in mucociliary clearance contribute to secretion retention and mucus plugging in the airways; a variety of techniques have been developed to optimize the removal of secretions and mucus.[115]

Respiratory therapy

Despite the lack of consistent evidence,[116,117] airway clearance techniques are the standard treatment for people with bronchiectasis.[47,118] Among independently performed techniques, active cycle of breathing, thoracic expansion exercises, forced expiration techniques, and autogenic drainage are recommended. These techniques can be aided by postural drainage and by modified postural drainage (postural drainage without head-down tilt). In addition, there are device-dependent techniques: positive expiratory pressure and intrathoracic oscillating positive expiratory pressure—the Flutter® (Scandipharm, Birmingham, AL, USA) and the Acapella® (Smiths Medical, Dublin, OH, USA); and extrathoracic oscillations—high-frequency chest wall oscillation with a vest (high-frequency airway clearance).[47,115,117,119] During an infectious exacerbation or when the patient is very fatigued, manual techniques can be offered as part of the airway clearance technique regimen.[47]

The use of intermittent positive pressure breathing lacks direct supporting evidence; however, this technique has been used as an adjuvant to reduce the work of breathing, increase tidal volume, and mobilize secretions, being used for supporting critically ill patients with airway clearance difficulties.[47,115] The choice of a technique should take into consideration patient preference, patient adherence, impacts on daily life, and presence of comorbidities.[85]

Our recommendation:

Respiratory therapy techniques for improving mucociliary clearance should be applied and taught to all bronchiectasis patients with chronic production of secretions and/or (CT scan) signs of mucus plugging.

Physical exercise/pulmonary rehabilitation

In a systematic review[120] on pulmonary rehabilitation (exercise and education) or exercise training in bronchiectasis patients, four trials with 164 participants were included. Incremental shuttle walk distance and quality-of-life scores were found to improve after the intervention, but these benefits were not sustained at 6 months. There was no effect on cough- or symptom-related quality of life. The frequency of exacerbations over 12 months was reduced with exercise training, but pulmonary rehabilitation initiated during an exacerbation had no impact on exacerbation frequency or mortality. The authors concluded that pulmonary rehabilitation and exercise training programs produce short-term improvements in exercise capacity.

One study on pulmonary rehabilitation (8 weeks of supervised exercise training and review of physical therapy techniques) reported reduced frequency of exacerbations over a 12-month follow-up period and extended time to first exacerbation.[121]

European[15] and Spanish[85] guidelines recommend that patients who have exertional limitation (mMRC scale score > 1) should be encouraged to exercise regularly and participate in pulmonary rehabilitation programs.

Our recommendation:

Refer bronchiectasis patients with exertional limitation for regular exercise and participation in pulmonary rehabilitation programs, if available.

Osmotic agents

Infection and inflammation reduce airway surface fluid height, impairing mucociliary clearance. There are two hyperosmolar agents with mucoactive properties: hypertonic saline and mannitol. However, even 0.9% saline may have mucoactive properties. Evidence suggests that 6-7% hypertonic saline changes sputum rheology, enabling better clearance by the cilia.[122]

A systematic review[123] identified two studies that showed that the use of hypertonic saline brings benefits. Inhaled hypertonic saline (7%) as an adjuvant to respiratory therapy for 4 weeks was more effective in promoting expectoration than was isotonic saline.[124] In another study, the use of hypertonic saline compared with 0.9% saline improved quality of life and pulmonary function, as well as reduced emergency room visits.[125] However, a 12-month study comparing the use of hypertonic saline with 0.9% saline showed that there were no differences in exacerbation rates, quality-of-life scores, FEV_1, or reduction in bacterial colonization of sputum.[126] Although there is no commercial formulation of hypertonic saline (6% or 7%) on the market in Brazil, hypertonic saline can be easily prepared at pharmacies.

A systematic review[123] identified five studies on the use of mannitol in adults, showing benefits in mucus clearance and in expectoration properties. However, those studies had very small samples. In a study involving 461 patients, inhaled mannitol (400 mg) was tested for 12 months in bronchiectasis patients. During the study period, there was no reduction in the exacerbation rate; however, there was improvement in quality of life and in the time to first exacerbation.[127]

Our recommendation:

The use of hypertonic saline (6-7%) should be considered in bronchiectasis patients with persistent secretions despite other measures. The first administration of hypertonic saline should be supervised to assess for adverse effects (bronchospasm), which can be prevented or minimized by prior administration of a short-acting bronchodilator.

Mucolytics

There is no evidence to support the use of N-acetylcysteine or guaiafenesin in bronchiectasis.[122,123]

Mucokinetic agents such as beta-agonists have the potential to improve mucociliary clearance.[128] European guidelines[15] recommend trying using mucolytics for 3 months for patients who have difficulty expectorating and therefore have a poor quality of life.

There are only two randomized studies that have analyzed the use of DNase.[68,129] The first[129] did not identify significant changes in spirometry, quality of life, dyspnea, or mucus transportability. The second[68] showed that the rates of pulmonary exacerbation and the decline in FEV_1 were significantly greater in the group treated with DNase.

Our recommendation:

There is insufficient evidence to recommend the routine use of mucolytics in bronchiectasis patients. The use of DNase is contraindicated for adult non-cystic fibrosis bronchiectasis patients.

Vaccines

Bronchiectasis patients are at an increased risk of developing pneumonia and having a high number of exacerbations of viral etiology.[130] Influenza caused by Influenza A and B virus increases the morbidity and mortality of patients with chronic diseases, as well as predisposing them to secondary bacterial pneumonia.[131] A prospective observational study evaluated 3,495 inpatients with community-acquired pneumonia (CAP) between 2000 and 2011.[132] Patients with non-cystic fibrosis bronchiectasis and CAP represented 2% of the sample and had characteristics and clinical results similar to those of the other patients. Despite the high prevalence of *P. aeruginosa* as the etiologic agent of CAP, *Streptococcus pneumoniae* was the most commonly isolated agent (44.4% vs. 42.7%; p = 0.821). This finding motivated the authors to recommend influenza and pneumococcal vaccination for bronchiectasis patients.[132]

Two types of influenza vaccines are regulated and available for use in Brazil, the trivalent and quadrivalent influenza vaccines,[133] and all patients with chronic respiratory diseases should be vaccinated annually, unless they have a contraindication.[134]

With regard to pneumococcal vaccines, the Brazilian Immunization Association and the SBPT recommend the following sequence for patients with chronic lung diseases: 13-valent pneumococcal conjugate vaccine (PCV13), which has stronger immunogenic effect, and, 1 year later, 23-valent pneumococcal polysaccharide vaccine (PPSV23); the PPSV23 can be boosted by a second dose administered 5 years after the first dose. If the individual has been vaccinated with PPSV23, it is appropriate to wait 1 year after PPSV23 before giving a dose of PCV13.[134]

Our recommendation:

Bronchiectasis patients should receive influenza vaccine annually and should receive PCV13 and PPSV23 in the sequence recommended by the Brazilian Immunization Association and the SBPT.

Treatment of chronic respiratory failure

Home oxygen therapy and noninvasive ventilation

PaO_2 < 60 mmHg is indicative of severe bronchiectasis and the possible need for long-term home oxygen therapy (18-24 h per day). Oxygen therapy may delay the onset of *cor pulmonale*, one of the factors related to morbidity and mortality in this specific group of patients, in addition to hypoxemia and hypercapnia.[135]

The indications for home oxygen therapy should be the same as those for chronic airway diseases, that is, PaO_2 < 55 mmHg or SpO_2 < 88% on room air or PaO_2 between 56 and 59 mmHg associated with *cor pulmonale* and/or hematocrit > 55%.[136]

Noninvasive mechanical ventilation may be indicated in patients with chronic respiratory failure with hypercapnia, as an adjuvant treatment to cardiopulmonary rehabilitation and respiratory therapy, as well as being indicated as supportive therapy in patients waiting for lung transplantation. It should be emphasized that noninvasive mechanical ventilation should be used with caution or should even be contraindicated if there is excessive bronchopulmonary secretion; noninvasive mechanical ventilation is therefore indicated mainly for phases that are clinically stable from a secretion point of view. Among the different possible modes of noninvasive mechanical ventilation, the most convenient is bilevel positive airway pressure (BiPAP).[15,85]

Our recommendation:

In patients with chronic hypoxemia despite optimal clinical treatment, long-term home oxygen therapy is indicated. In clinically stable patients with chronic hypercapnic respiratory failure, noninvasive mechanical ventilation by BiPAP should be used as an adjuvant to cardiopulmonary rehabilitation and respiratory therapy.

Lung transplantation

Lung transplantation is indicated for adult individuals with chronic, end-stage lung disease or evidence of disease progression who are at a high (> 50%) risk of death within 2 years despite full optimal treatment, unless they have an absolute contraindication.[85,137] There are no specific recommendations on the timing of referring non-cystic fibrosis bronchiectasis patients for lung transplantation, which means that the recommendations are based on those proposed for other chronic lung diseases and for bronchiectasis associated with cystic fibrosis.[137,138]

Lung transplantation should be considered for individuals with diffuse bronchiectasis who have a progressive decline in pulmonary function despite full clinical treatment.[139,140] Progression of the underlying disease with severe impairment of pulmonary function (FEV_1 < 30% of predicted); presence of hypoxemia (requiring home oxygen therapy) and hypercapnia; need for noninvasive ventilation; severe exacerbations and frequent hospitalizations; and development of pulmonary hypertension are signs that the patient should be referred for lung transplantation.[85,139,141]

In three series of transplant recipients, 1-, 5-, and 10-year survival was, respectively, between 68% and 85%,[142-144] between 61% and 73%,[142-144] and 48%.[143] In those studies, (sequential) bilateral transplantation was more common than unilateral transplantation. Since bronchiectasis is a suppurative lung disease, bilateral transplantation is always indicated.

Our recommendation:

Lung transplantation should be considered for patients with FEV_1 < 30% of predicted or for those with higher FEV_1 values but with rapid lung function decline. Some factors, if present, should alert to the possibility of early referral of the patient for lung transplantation evaluation. These factors include severe and frequent exacerbations, with ICU admissions; recurrent or treatment-refractory pneumothorax or hemoptysis; chronic respiratory failure; and hypercapnia or pulmonary hypertension.

Surgical treatment

Surgical resection is a potentially curative treatment for patients with localized disease refractory to clinical treatment. Palliative surgical treatment (diffuse disease) should be reserved only for cases of severe hemoptysis with ineffective embolization or cases of abscessed areas unresponsive to antimicrobial treatment and associated measures.[15,145]

Lobectomy in chronic inflammatory lung diseases can be performed safely by thoracoscopy, and the rate of conversion to thoracotomy is low.[146,147] Surgery by video-assisted thoracoscopy reduces hospital stays and has a lower rate of complications, especially with regard to bleeding, when compared with surgery by thoracotomy.[148]

In a specific group of patients with focal disease unresponsive to clinical treatment, resection was associated with a significant improvement in symptoms and an acceptable risk of morbidity and mortality.[149] A meta-analysis revealed a mortality rate of 1.5% and an improvement in symptoms in 66.5% of patients.[145] In one study, quality of life after 1 year of follow-up was reported as excellent in 73.3% of patients and as unchanged in only 8.3%.[150] One group of authors also demonstrated that quality of life improved and exercise capacity was preserved in selected surgical patients.[151] The presence of residual bronchiectasis, nontuberculous mycobacterial infection, or immunosuppression can be risk factors for poor clinical response after surgery. The underlying disease is also a determinant of therapeutic decision.[145,152]

Our recommendation:

Surgical treatment should be reserved for individuals with localized bronchiectasis refractory to clinical treatment, and video-assisted thoracoscopy is the procedure of choice.

THERAPEUTIC MANAGEMENT OF EXACERBATIONS

Definition and role of exacerbations

An exacerbation is characterized by worsening of three or more of the following symptoms for at least 48 h: 1) cough; 2) sputum volume or viscosity; 3) sputum purulence; 4) dyspnea or exercise intolerance; 5) fatigue; and 6) hemoptysis.[153]

Chest X-ray may show preexisting bronchiectasis filled with secretion, with no signs of consolidation. The diagnosis is clinical, and ancillary tests can be used for differential diagnoses, such as pneumonia, pneumothorax, pulmonary thromboembolism, and heart diseases.

The causes of exacerbations are not fully understood, but a relationship is known to exist between chronic bronchial bacterial infection and inflammation. Viral infections or other bacteria can trigger an imbalance in this relationship.[10,154]

In addition to having a major impact on patient quality of life, exacerbations increase health care costs. Another important consequence is higher mortality rates, since patients with more than three exacerbations or a hospitalization in the previous 12 months experience increased mortality.[155,156]

Severity of exacerbations

Once an exacerbation is diagnosed, history taking and physical examination should be targeted at determining the severity of the attack. Severe exacerbations require intravenous antibiotic therapy and/or hospitalization. Signs indicating the severity of an exacerbation are as follows[47,85,157]: respiratory rate ≥ 25 breaths/min; respiratory distress with use of accessory muscles; deterioration of oxygen saturation; cyanosis; body temperature ≥ 38°C; or another criterion for sepsis and hemoptysis (> 25 mL in 24 h). Patients with hemodynamic instability, an altered level of consciousness, or mental confusion should be considered for ICU treatment. Unavailability of home intravenous therapy may lead to the need for hospitalization in patients who used oral antibiotics and showed no response to treatment.

It is of note that chronic infection with *P. aeruginosa* is associated with more frequent hospital admissions, longer hospital stays, worse pulmonary function, and higher mortality.[73,158] Therefore, patients with chronic infection with *P. aeruginosa* should be carefully evaluated for exacerbation severity.

Among inpatients, predictors of higher mortality include male gender, use of systemic corticosteroids, low FEV_1, increased creatinine, history of smoking, and need for mechanical ventilation.[159]

Treatment of exacerbations

Choice of antibiotic therapy

The use of antibiotics is essential for treating exacerbations in bronchiectasis. Upon diagnosis of an

exacerbation, sputum sample collection is indicated, but treatment initiation should not wait for results, which will be used only if the patient does not respond adequately to the initially chosen treatment. The choice of an antibiotic regimen should take into consideration results of previous aerobic sputum cultures and response to antibiotics in previous exacerbations, as illustrated in Figure 7. Regardless of the antibiotic chosen, it is always suggested that the maximum recommended doses be used in order to ensure better penetration of the drug into dilated, structurally altered airways with accumulation of secretions.

Duration of treatment

Few studies have evaluated the duration of treatment for exacerbations. Currently, 14-day to 21-day treatment courses are recommended. In mild cases, in which the patient rapidly returns to baseline symptoms after treatment initiation, a treatment course of only 10 days can be considered.[15]

There is no literature evidence on which outcomes are the best for use in determining the resolution of exacerbations. For patients with severe exacerbations, it is recommended that clinical improvement be associated with inflammatory markers and pulmonary function (spirometry or PEF). There is a significant increase in leukocytes, neutrophils, CRP, and fibrinogen in exacerbations; however, a small percentage of patients do not show inflammatory improvement by the end of treatment. Pulmonary function declines in exacerbations, and often recovers within 2 weeks of treatment completion. The greater the decline is, the greater is the risk of a long recovery period.[160-162]

Other therapeutic measures

There is little evidence to support the use of other medications and adjuvant measures; however, some may be considered in specific situations:

- Systemic corticosteroids: Systemic corticosteroids should be used if there is associated asthma or

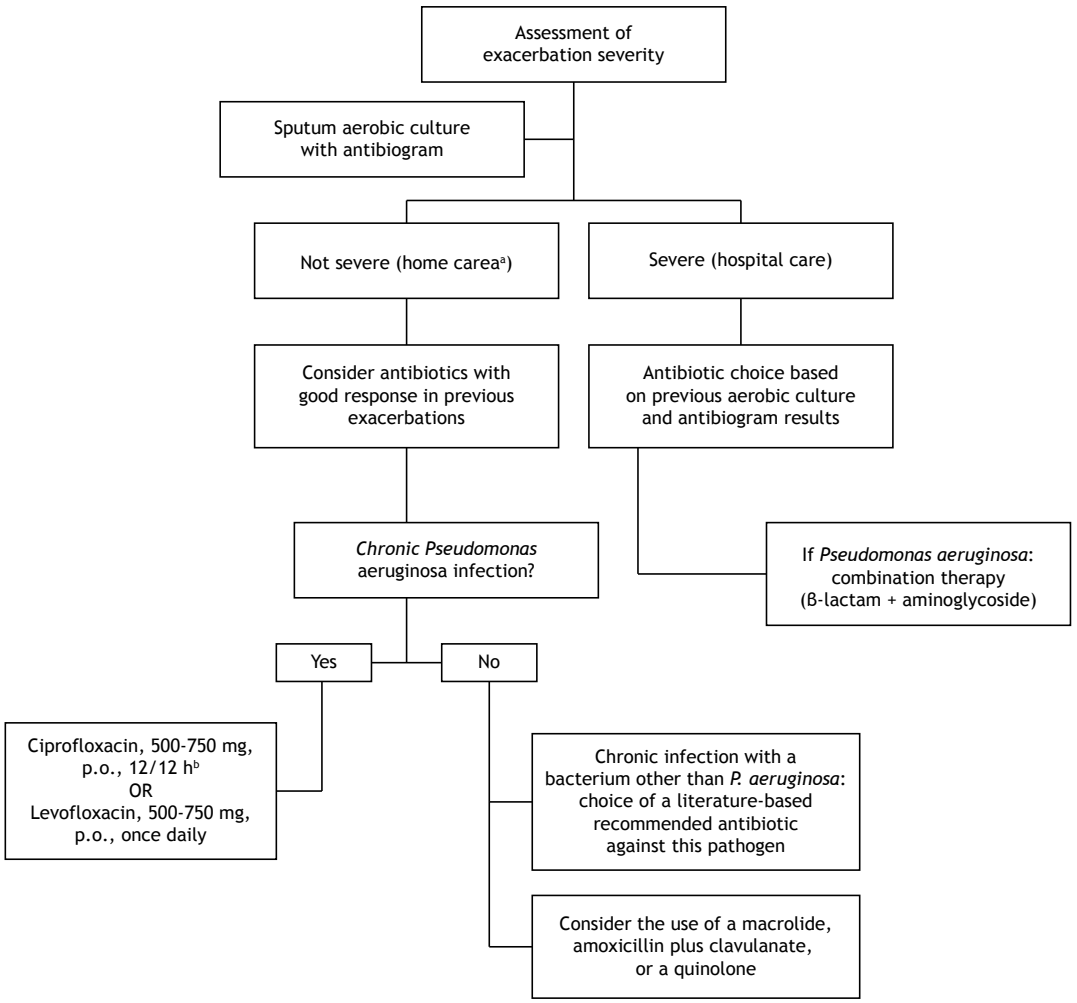

Figure 7. Flow chart for the therapeutic management of exacerbations. [a]If intravenous treatment is necessary in non-severe exacerbations, consider the possibility of intravenous administration at home. [b]The dose of ciprofloxacin, 750 mg, 12/12 h should be reserved for severe exacerbations in patients weighing more than 50 kg.

COPD. They may be considered in patients with hypersecretion, at low doses (0.25 to 0.5 mg/kg of prednisone or equivalent), with attention being paid to the risks of side effects.

- Inhaled bronchodilators: Inhaled bronchodilators may be added to treat patients with significant dyspnea, especially during hospitalization, always taking into consideration the possible adverse events.
- Respiratory therapy: It is recommended that exercises for bronchial hygiene be increased during an exacerbation, regardless of the technique usually used by the patient. In cases of hospitalization, daily follow-up with a physical therapist, at least two sessions per day, is indicated.
- Hyperosmolar agents: Hyperosmolar agents may be considered in order to improve bronchial hygiene. The most commonly used option is hypertonic saline, starting at 3%, with the possibility of increasing up to a concentration of 7% if well tolerated. Because of the risk of hyperosmolar-induced bronchospasm, rapid-onset bronchodilators should be used 15-30 min prior to inhalation and the patient should be supervised when using a hyperosmolar agent for the first time.

Inhaled antibiotics: Inhaled antibiotics are not routinely recommended for the treatment of exacerbations. If the patient is already using chronic inhaled antibiotics, he/she can continue the medication as long as the risks of side effects from concurrent use of inhaled and systemic antibiotic therapy are assessed.[163,164]

Our recommendation:

Once an exacerbation is diagnosed, the severity of the exacerbation should be determined in order to decide between home care and hospitalization. Before initiating antibiotic therapy (based on previous culture results), another sputum sample should be collected for microbiological analysis, the results of which will be used if there is no response to treatment. Adjuvant measures (use of corticosteroids, bronchodilators, respiratory therapy, and/or hypertonic agents) should be instituted based on clinical judgment.

FINAL CONSIDERATIONS

Chart 6 summarizes the recommendations for the follow-up and treatment of non-cystic fibrosis bronchiectasis patients.

Chart 6. Chart of recommendations for follow-up and treatment of non-cystic fibrosis bronchiectasis patients.

Recommendations			
Follow-up	Functional aspects		Perform spirometry with bronchodilator use every 6 months, lung volume assessment (if available) annually, and the six-minute walk test (at the physician's discretion).
	Microbiologic aspects		Collect samples from the lower respiratory tract (sputum, for example) at regular intervals of 3-4 months and during pulmonary exacerbations for aerobic culture, as well as annually for culture for fungi and mycobacteria. If the patient is being treated with chronic macrolide therapy, culture for mycobacteria should be performed every 6 months.
	Systemic markers		Although CRP appears to be an inflammation-related marker and is available for use in clinical practice, there is insufficient evidence to recommend its routine use to assess disease severity.
	Severity and prognostic scores		A severity score and a prognostic estimate should be calculated at the time patients are diagnosed with bronchiectasis. Periodic calculation of the score (annually, for example) aids in therapeutic management. To date, the FACED and the E-FACED scores are the ones that have been validated for use in Brazil.
Treatment of stable patients	Chronic airway infection	Primary infection	Immediately following the first identification of *P. aeruginosa* in the sputum of a patient, the patient should be treated with a systemic antipseudomonal antibiotic combined with an inhaled antibiotic. Follow-up sputum culture is recommended 2-4 weeks after treatment completion.
		Chronic bronchial infection	Bronchiectasis patients with chronic *Pseudomonas aeruginosa* infection and exacerbations may benefit from and should be treated with long-term inhaled antibiotics. The choice will depend on the availability of and access to medication.

CRP: C-reactive protein; FACED: acronym for **E**xacerbation, **F**EV$_1$, **A**ge, **C**hronic colonization with *Pseudomonas aeruginosa*, **E**xtent (of CT findings), and **D**yspnea; BD: bronchodilator; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; SBIm: *Sociedade Brasileira de Imunização* (Brazilian Immunization Association); SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association); and BiPAP: bilevel positive airway pressure.

Chart 6. Continued...

Recommendations			
	Chronic inflammation	Macrolides	Use macrolides as continuous therapy for at least 6-12 months for bronchiectasis patients with at least two exacerbations per year. Prefer azithromycin. The use of macrolides may be considered, although there is no evidence, for patients with fewer than two exacerbations per year but with a history of severe exacerbations or primary or secondary immunodeficiency, those whose exacerbations have a significant impact on their quality of life, and those with more severe bronchiectasis. Active nontuberculous mycobacterial infection should be ruled out.
		Inhaled corticosteroids	There is insufficient evidence to support the routine use of inhaled corticosteroids in adults with bronchiectasis. Inhaled corticosteroid therapy may be justified in some subgroups of adults if there is associated asthma or COPD.
	Bronchodilators		There is insufficient data to recommend the routine use of BDs in bronchiectasis patients without dyspnea. Long-acting BDs may be recommended if bronchiectasis is associated with asthma or COPD. Because of the potential risk of bronchospasm resulting from the use of inhaled mucoactive drugs and inhaled antibiotics, it is suggested that BDs be used prior to using these drugs.
	Airway clearance	Respiratory therapy	Respiratory therapy techniques for improving mucociliary clearance should be applied and taught to all bronchiectasis patients with chronic production of secretions and/or (CT scan) signs of mucus plugging.
		Physical exercise and pulmonary rehabilitation	Refer bronchiectasis patients with exertional limitation for regular exercise and participation in pulmonary rehabilitation programs, if available.
		Osmotic agents	The use of hypertonic saline (6-7%) should be considered in bronchiectasis patients with persistent secretions despite other measures. Hypertonic saline should be first administered under supervision to assess for adverse effects (bronchospasm), which can be prevented or minimized by prior administration of a short-acting bronchodilator.
		Mucolytics	There is insufficient evidence to recommend the routine use of mucolytics in bronchiectasis patients. The use of DNase is contraindicated for adult non-cystic fibrosis bronchiectasis patients.
	Vaccines		Bronchiectasis patients should receive influenza vaccine annually and should receive PCV13 and PPSV23 in the sequence recommended by the SBIm and the SBPT.
	Chronic respiratory failure	Home oxygen therapy and noninvasive ventilation	In patients with chronic hypoxemia despite optimal clinical treatment, long-term home oxygen therapy is indicated. In clinically stable patients with chronic hypercapnic respiratory failure, noninvasive mechanical ventilation by BiPAP should be used as an adjuvant to cardiopulmonary rehabilitation and respiratory therapy.
		Lung transplantation	Lung transplantation should be considered for patients with FEV_1 < 30% of predicted or for those with higher FEV_1 values but with rapid lung function decline. Some factors, if present, should alert to the possibility of early referral of the patient for lung transplantation evaluation. These factors include severe and frequent exacerbations, with ICU admissions; recurrent or treatment-refractory pneumothorax or hemoptysis; chronic respiratory failure; and hypercapnia or pulmonary hypertension.

CRP: C-reactive protein; FACED: acronym for **E**xacerbation, **F**EV_1, **A**ge, **C**hronic colonization with *Pseudomonas aeruginosa*, **E**xtent (of CT findings), and **D**yspnea; BD: bronchodilator; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; SBIm: *Sociedade Brasileira de Imunização* (Brazilian Immunization Association); SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association); and BiPAP: bilevel positive airway pressure.

Chart 6. Continued...

Recommendations	
Surgical treatment	Surgical treatment should be reserved for individuals with localized bronchiectasis refractory to clinical treatment, and video-assisted thoracoscopy is the procedure of choice.
Treatment of exacerbations	Once an exacerbation is diagnosed, the severity of the exacerbation should be determined in order to decide between home care and hospitalization. Before initiating antibiotic therapy (based on previous culture results), another sputum sample should be collected for microbiological analysis, the results of which will be used if there is no response to treatment. Adjuvant measures (use of corticosteroids, bronchodilators, respiratory therapy, and/or hypertonic agents) should be instituted based on clinical judgment.

CRP: C-reactive protein; FACED: acronym for **E**xacerbation, **F**EV$_1$, **A**ge, **C**hronic colonization with *Pseudomonas aeruginosa*, **E**xtent (of CT findings), and **D**yspnea; BD: bronchodilator; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; SBIm: *Sociedade Brasileira de Imunização* (Brazilian Immunization Association); SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association); and BiPAP: bilevel positive airway pressure.

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Video-assisted thoracoscopic thoracic duct ligation with near-infrared fluorescence imaging with indocyanine green

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TO THE EDITOR:

Surgical ligation of the thoracic duct can be a challenging procedure. If a chyle leak can be identified, direct ligation with nonabsorbable suture should be performed.[1] In cases in which the chyle leak or the duct itself cannot be identified, mass ligation of the duct performed above the esophageal hiatus is the approach of choice.[2] This ensures duct ligation at its entry in the chest, thus sealing all of the accessory ducts that could be the source of the chylothorax.[2,3] Thoracic duct ligation (TDL) is typically performed by means of thoracoscopy, which allows image magnification and facilitates identification of the site of chyle leak.[1] Enteral administration of a fat source such as olive oil or cream during the procedure can be used in order to assist in locating the site of leak by increasing the flow of chyle.[1] Invisible near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) is a new imaging modality that combines NIR imaging and a fluorescent dye (ICG) to improve visualization during surgery. NIR fluorescence imaging with ICG allows visualization of the light emitted from the dye, which is then superimposed onto the video image, thus highlighting the fluorescence site.[4] Below, we describe the case of a patient in whom NIR fluorescence imaging with ICG was used.

A 55-year-old male patient was diagnosed with oropharyngeal squamous cell carcinoma with left cervical lymph node involvement. Six months after having undergone treatment with carboplatin and paclitaxel followed by radiation therapy (70 Gy), the patient experienced lymph node disease recurrence. Radical neck dissection was therefore performed. Three days after the procedure, a chest X-ray showed pleural effusion. The effusion was sampled. Pleural fluid analysis showed elevated triglyceride levels (of 450 mg/dL), which were consistent with a chylothorax. Pleural drainage was therefore performed. On the same day, fluid draining from the cervical wound was analyzed and found to be consistent with chyle. The patient was started on a regular medium-chain triglyceride diet and responded well to treatment, as evidenced by a reduction in fluid output from the chest tube and the cervical drain, both of which were removed four days later. The patient was discharged two days after the chest tube and the cervical drain had been removed. One week later, he returned to the emergency room with a neck lump (Figures 1A, B, and C). A chest X-ray was normal. Percutaneous catheter drainage was performed. The fluid had a milky appearance and elevated triglyceride levels (of 350 mg/dL). Because management with oral fasting, parenteral nutrition, and octreotide therapy for 15 days failed, a decision was made to perform a TDL. For better visualization of the thoracic duct, 50 mL of olive oil were administered enterally 60 min before the procedure. Under general anesthesia, the patient underwent three-port video-assisted thoracoscopic TDL with ICG-assisted NIR fluorescence imaging, a PINPOINT® endoscopic fluorescence imaging system (Stryker Corporation, Kalamazoo, MI, USA) being used. With the use of ultrasound to identify inguinal lymph nodes, 2 mL of 0.5% ICG solution were injected bilaterally. Approximately 5 min after local massage, the thoracic duct was visible as green fluorescence, no chyle leak being present (Figure 1D). Metal clips were used for TDL (Figure 1E). The patient made an uncomplicated recovery. The chest tube was removed two days after the procedure, and the patient was discharged four days after the procedure. There was no recurrence of the chylous fistula.

ICG is a disulfonated heptamethine indocyanine small molecule that has been approved by the US Food and Drug Administration for cardiac output monitoring, liver function testing, hepatic blood flow measurement, and ophthalmic angiography.[5] ICG binds to plasma lipoproteins and is activated by NIR rays of 760-780 nm, resulting in fluorescence. It has an extremely small hydrodynamic diameter, which allows it to travel through blood vessels, lymph nodes, and lymphatic ducts.[5] The development of equipment that allows fluorescent images to be superimposed onto video images in real time allowed ICG to be used in many surgical applications, including evaluation of flap perfusion, evaluation of anastomotic perfusion, identification of anatomical structures (such as blood vessels, biliary vessels, and lymphatic vessels), and identification of lymphatic drainage in cancer surgery.[6,7] In thoracic surgery, NIR fluorescence imaging with ICG can be used for identification of lung nodules, identification of the intersegmental plane, and conduit vascular evaluation during esophagectomy.[4] According to Ashitate et al.,[5] injection of ICG into the lower leg of pigs provided thoracic duct imaging with an onset of approximately 5 min after injection, as well as sustained imaging for at least 60 min after injection. In addition, an injury

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model showed that it is possible to identify chyle leaks without loss of accuracy.[5]

The use of ICG for the clinical treatment of chylothorax is still relatively new.[8,9] Chang et al.[9] reported the case of a three-month-old infant with congenital heart disease and postoperative chylothorax. During repeat sternotomy, no chyle leak was found. NIR fluorescence imaging with ICG allowed visualization and treatment of a fistula in an unusual location (i.e., lateral to the aorta). Kaburagi et al.[8] described the case of a patient in whom ICG was injected into the mesentery during transabdominal TDL for the management of postesophagectomy chylothorax.

In the case reported here, NIR fluorescence imaging with ICG was used in order to identify the thoracic duct, improving its visualization. The need for injecting ICG into lymph nodes represented a technical challenge, which was overcome with the use of ultrasound-guided injection. NIR fluorescence imaging with ICG provides excellent real-time intraoperative visualization of the thoracic duct, being particularly useful in cases in which identification of the thoracic duct or chylous fistula is likely to be difficult, including reoperations, procedures performed after radiation therapy, and procedures performed in children, as well as cases in which there is no active chyle leak in the chest.

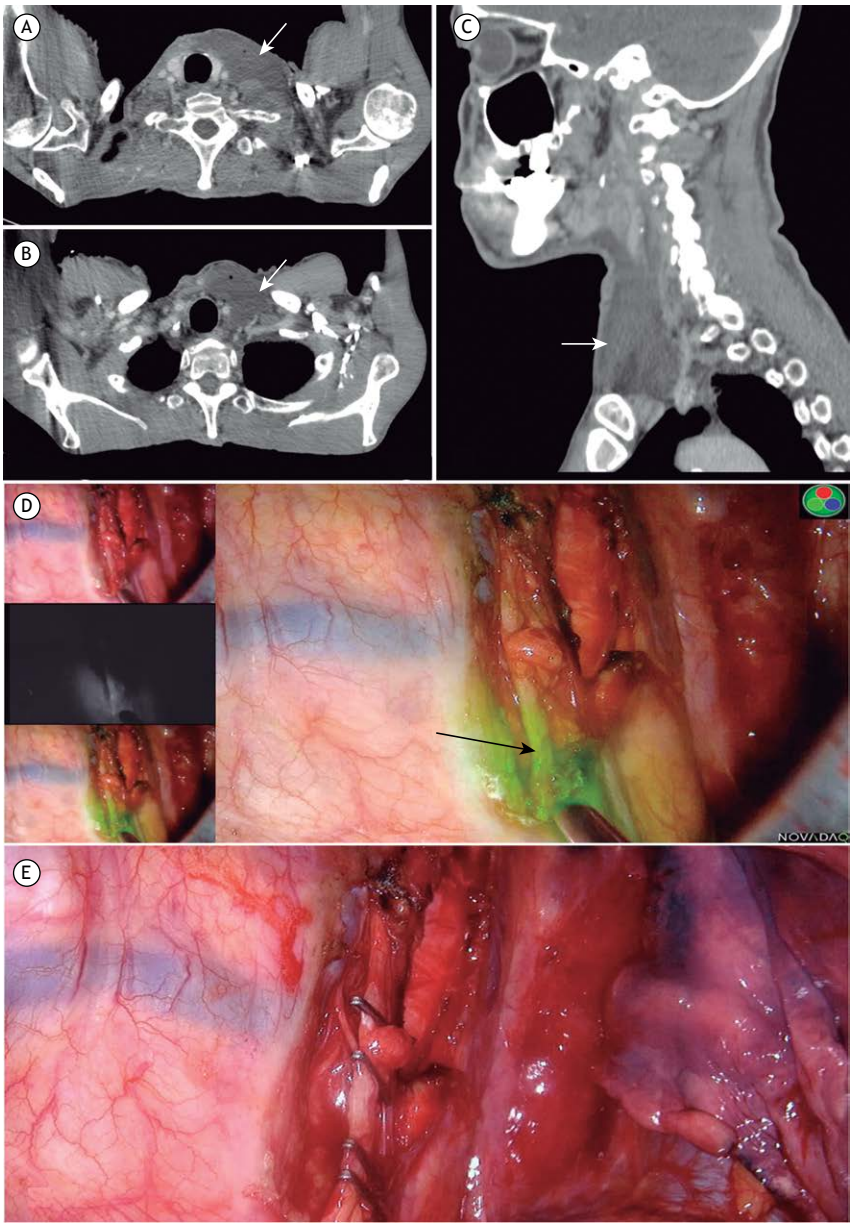

Figure 1. In A and B, CT scan of the neck showing a large fluid collection (arrow). In C, sagittal CT reconstruction. In D, intraoperative view of the thoracic duct dissected after injection of indocyanine green (arrow). In E, thoracic duct ligation with metal clips.

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Pulmonary benign metastasizing leiomyoma presenting as small, diffuse nodules

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TO THE EDITOR:

We report the case of a 46-year-old nonsmoking female patient with controlled asthma, under regular treatment with a combination of inhaled fluticasone and salmeterol. She presented with a one-year history of cough, wheezing, and dyspnea on moderate exertion. There was no history of weight loss, hemoptysis, chest pain, environmental exposure, or drug exposure. On physical examination, the uterus was palpable and firm, the uterine fundus being midway between the symphysis pubis and the umbilicus. The remainder of the physical examination was normal. Sputum examination, blood biochemistry, and tumor markers (including CA 19-9 and CA 125) were all normal. Spirometry showed mild obstructive lung disease and positive bronchodilator test results. Chest X-rays (Figure 1A) and chest CT scans (Figures 1B and 1C) showed numerous ill-defined, confluent, rounded, nodular opacities of 2-10 mm in diameter in both lungs. Bronchoscopy was normal. Bronchial lavage fluid cytology was negative for infectious and malignant etiologies. Transbronchial lung biopsy showed relatively ill-circumscribed nodules consisting of interlacing bundles of uniform spindle cells with oval nuclei and inconspicuous nucleoli in a background of collagen, the adjacent lung parenchyma being compressed (Figure 1D). Immunohistochemistry was positive for vimentin, smooth muscle actin, and desmin, as well as for estrogen and progesterone receptors, but was negative for cytokeratins and p63, the nodules therefore originating from uterine smooth muscle cells. The Ki-67 proliferation index was < 5%, which is typical of benign smooth muscle tumors. A diagnosis of benign metastasizing leiomyoma (BML) was made on the basis of histological and imaging findings. At this writing, the patient is receiving monthly treatment with goserelin acetate on an outpatient basis and undergoing preoperative evaluation for hysterectomy and oophorectomy.

Pulmonary BML is a rare condition characterized by benign uterine leiomyoma metastasizing to the lung. Although pulmonary BML is most commonly seen in women of reproductive age presenting with a history of uterine leiomyoma and undergoing hysterectomy, it can affect women who have not undergone hysterectomy, as was the case here. Metastatic spread is believed to occur through the blood. Although the lung is the most common metastatic site, BML can metastasize to the lymph nodes, central nervous system, mediastinum, bones, and heart.[1-4] Given that most patients are asymptomatic, pulmonary BML is usually an incidental finding on routine chest X-rays. However, patients with pulmonary BML can present with cough, hemoptysis, dyspnea, and reduced lung function. Typical imaging findings include multiple

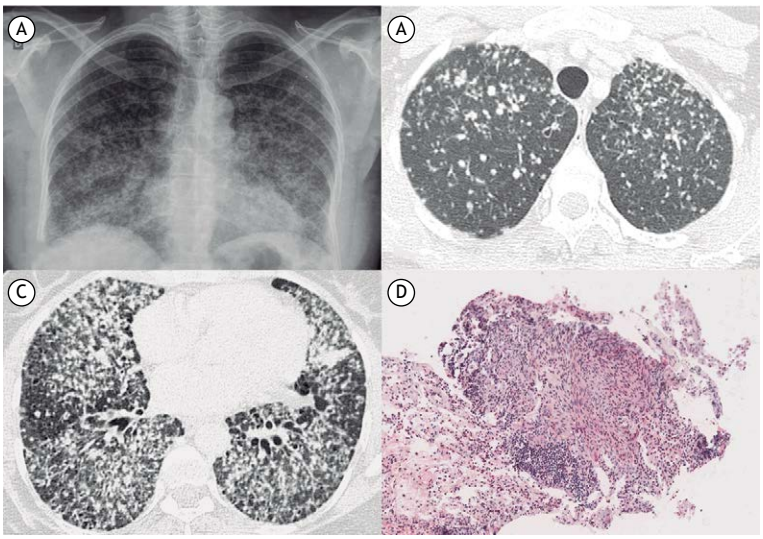

Figure 1. In A, posteroanterior chest X-ray showing diffuse infiltration of the lung parenchyma by small pulmonary nodules. In B and C, axial CT scans showing confluent nodules of varying sizes with irregular margins. In D, histological staining showing a nodule with ill-defined margins, consisting of interlacing bundles of spindle-shaped cells without atypia, with low mitotic activity and without necrosis (H&E; magnification, ×10).

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(but no more than ten) pulmonary nodules of varying sizes. However, pulmonary BML can present as cystic, cavitary, or miliary lesions.[2-4] Metastatic uterine leiomyosarcoma is the main differential diagnosis.[2] Surgical biopsy with immunohistochemical staining is the gold standard for the diagnosis of pulmonary BML.[2,5] In the case reported here, the histopathological features were characteristic of pulmonary BML, including interlacing bundles of smooth muscle cells without vascular invasion or cellular atypia, as well as very low mitotic activity. Multiple treatment options have been described, including watchful waiting, surgical resection, and antiestrogen therapy.[2] BML tends to have an indolent course and a favorable outcome, and can regress spontaneously after menopause, although lung lesions can continue to progress, leading to pulmonary insufficiency and even death.[2,4]

It is of note that, in our patient, lung lesions occurred concomitantly with uterine leiomyoma rather than having developed from it, as is commonly reported. The number of small, confluent nodules is also of note, being much higher than that reported in the literature.

In conclusion, BML should be included in the differential diagnosis of micronodules and diffuse pulmonary nodules in women. Attending physicians should collect information on symptoms and gynecological history in order to screen for uterine leiomyoma.

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Occupational exposure to dust: an underestimated health risk?

Sandra Saleiro[1,a], Luís Rocha[1,2,b], João Bento[1,2,c], Luís Antunes[3,d], José Torres da Costa[4,e]

TO THE EDITOR:

Occupational exposure to dust, even at low doses, is a risk to workers' health because it is significantly associated with respiratory symptoms. It is known that the length of exposure to airborne substances (dust, gases, vapors, or chemicals) is directly related to the likelihood of respiratory problems, as well as that of asthma, lung cancer, hypersensitivity pneumonitis, and other interstitial lung diseases.[1,2]

Despite the fact that, in most industries, air quality evaluations are carried out on a regular basis and the legislated exposure limits are being respected, workers sometimes have health complaints that might be attributable to occupational exposure to dust.[3,4] Therefore, we decided to apply a questionnaire to assess the impact that occupational exposure to dust has on the development of respiratory symptoms among workers at an automobile parts manufacturer in northern Portugal. At this writing, the factory is owned by a multinational group dedicated to the research, development, and production of equipment for the automotive industry, employing approximately 1,000 permanent workers and another 200 temporary workers. Most (85%) of the employees work in the production area, where there is dust formation, as well as vaporization and aerosolization of oil waste. The production cycle begins with the winding of wire into a spiral which is then coated with a plastic composite, under very high pressure with intense friction, producing a large amount of dust. The cables are then cut, and plastic or zamak (a zinc-aluminum-magnesium-copper alloy) is applied by injection. That process generates particulate matter: total dust (0-25 μm); breathable dust (0-10 μm); and volatile organic compounds, which have a particle phase. According to Portuguese law, periodic evaluation of the concentrations of particulate matter in the workplace atmosphere is required.[4,5] Specifically at the factory in question, there were air exhaust systems installed in the manufacturing area and at the workstations where the risk of exposure is highest. In addition, there were annual measurements of total dust, respirable dust, and concentrations of volatile organic compounds are measured by a certified external laboratory, including gravimetric measurement (weighing of filters), with air samples taken on a working day at the workstations with the highest exposure risk (i.e., those in the spiral manufacturing, extrusion, cutting, and injection areas). Results are then compared to the exposure limits defined by Portuguese regulation.[4]

Over a 1-month period, the occupational health and safety department of the company provided each worker with a non-anonymous, voluntary, self-report questionnaire about the presence of ocular, nasal, and respiratory symptoms (including coughing fits, chest tightness, breathlessness, and dyspnea) and their relationship with the working period (yes/no questions). We chose to use a symptoms questionnaire because it is a simple, easily implemented, inexpensive way to obtain information on worker health status and is easily reproducible for occupational disease screening. Because there is no validated questionnaire for evaluating respiratory symptoms in the workplace in Portugal, the questionnaire used was adapted from the British Medical Research Council scale (1976 version) and the Control of Allergic Rhinitis and Asthma Test, which has been validated for use in adults in Portugal.[6]

The clinical files of the respondents were analyzed for demographic data, workstation type, duration of exposure to dust, history of respiratory diseases, smoking status, and most recent pulmonary function test results. The association between the presence of at least one respiratory symptom and the duration of exposure to dust was assessed by logistic regression.

A total of 207 workers completed the questionnaire: 58.5% were women; and the mean age was 38.7 years. Of those 207 employees, 161 (77.8%) worked in the production area, 38 (18.4%) worked in the logistics department; and 8 (3.8%) worked in the office. A total of 110 workers (53.1%) reported at least one respiratory symptom: ocular symptoms, in 48 (23.2%); nasal symptoms, in 67 (32.4%); coughing fits, in 48 (23.2%); chest tightness, in 40 (19.3%); breathlessness, in 41 (19.8%); and dyspnea, in 32 (15.5%). Of the 207 respondents, 31 (15.0%) reported having only one symptom, whereas 37 (17.8%) reported having two symptoms and 42 (20.3%) reported having three or more. Of the 110 workers who reported at least one symptom, 81 (73.6%) reported experiencing symptoms on working days and only 6 (5.5%) reported experiencing symptoms on their days off. When analyzing the clinical files of the respondents, we observed a median duration of exposure to dust of 9 years (7 years in men and 10 years in women), 97 (47%) of the respondents having worked at the company for more than 10 years, which

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Table 1. Multivariate analysis of symptoms and their association with the duration of exposure to dust.

Symptoms	OR	95% CI
Ocular	1.00	0.95-1.05
Nasal	1.02	0.96-1.07
Cough	0.96	0.91-1.02
Chest tightness	1.05	0.99-1.11
Breathlessness	1.04	0.98-1.10
Dyspnea	1.08	1.01-1.14

represents a significant duration of exposure to dust, especially for those who worked in the production area. Of the 207 respondents, 132 (63.7%) were nonsmokers, 67 (32.4%) were current smokers, and 8 (3.7%) were former smokers. The duration of exposure to dust correlated significantly with chest tightness, breathlessness, and dyspnea ($p = 0.012$, $p = 0.05$, and $p < 0.001$, respectively). In a multivariate analysis (logistic regression and the Wald test), after adjusting for possible confounders, such as a history of respiratory diseases and smoking, we found that only dyspnea retained a statistically significant correlation with the duration of exposure to dust ($p = 0.02$; Table 1). Although 31 (14.9%) of the respondents had impaired lung function, that was not influenced by the duration of exposure to dust ($p = 0.263$, Mann-Whitney test). Mild obstruction or obstruction of the small airways was the most common pattern in those workers, possibly related to asthma ($n = 5$) and smoking ($n = 21$). It was not possible to determine the relationship between the pattern of obstruction and exposure to dust, because of the small number of cases. The type of workstation did not have a statistically significant effect on the probability of respiratory symptoms. However, we must point out that most (77.8%) of the respondents worked in the production area, only 18.4% and 3.8% working in the logistics department and the office, respectively.

The symptoms evaluated in the present study were similar to those evaluated in other studies. In a study of workers exposed to free silica, Castro et al.[7] found a prevalence of respiratory symptoms similar to what was found in our study (cough in 30.5% and dyspnea in 11%), although the proportion of current or former smokers was higher (52%) in their sample.[7] Occupational exposure accounts for a substantial proportion (10-20%) of either symptoms or functional impairment consistent with COPD.[2]

We found that respiratory symptoms were more common on working days and that the duration of exposure to dust was an independent risk factor for dyspnea. Although the questionnaire employed was not designed to assess lung impairment, we found that the work environment was responsible for the respiratory symptoms reported in the studied population. Other studies analyzing the prevalence of respiratory symptoms and its association with occupational exposure have also reported the presence of upper and lower airway diseases.[8,9]

The present study demonstrates that, in addition to periodic measurements of air quality, increased efforts should be made to improve collective protection measures and to raise worker awareness regarding the proper use of personal protective equipment, in order to reduce the risks of exposure to dust. We cannot rule out the possibility that the symptoms reported in our study were related to inappropriate use of personal protective equipment, because that was not a focus of our analysis.

As a result of this study, the occupational health department of the company implemented a respiratory surveillance plan, including collective lectures about occupational risks, risk prevention, and safety rules, especially the proper use of personal protective equipment. Workers also undergo periodic medical evaluation for the early identification of any respiratory symptoms.

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A mobile calcified nodule in the pleural cavity: thoracolithiasis

Dante Luiz Escuissato[1,a], Gláucia Zanetti[2,b], Edson Marchiori[2,c]

A 50-year-old female smoker was referred to our hospital for evaluation of a pulmonary nodule seen on a chest X-ray during a routine check-up. She was asymptomatic from a respiratory point of view. The physical examination findings and laboratory test results were unremarkable. Chest CT demonstrated the presence of a calcified nodule in the left pleural cavity (Figures 1A and 1B). Follow-up CT scans obtained 1 year later showed that the nodule was mobile, and had migrated laterally (Figures 1C and 1D). That finding was considered to be diagnostic of thoracolithiasis.

Thoracolithiasis is a rare benign condition characterized by the presence of one or more mobile free bodies, with or without calcification, in the pleural cavity. Thoracolithiasis is rarely symptomatic, and most cases are diagnosed on the basis of an incidental finding on an X-ray, on a CT scan, during surgery, or at autopsy. Mobility of the body (nodule), as demonstrated by sequential imaging studies, is the most characteristic finding. Although most such nodules are found to be mobile during follow-up, some are immobile and difficult to diagnose. Thoracolithiasis does not require any specific treatment, especially not surgical resection.[1-3] For patients with mobile pleural calcified nodules, clinicians and radiologists should recommend clinical observation, because nodule removal might not be necessary for diagnosis.

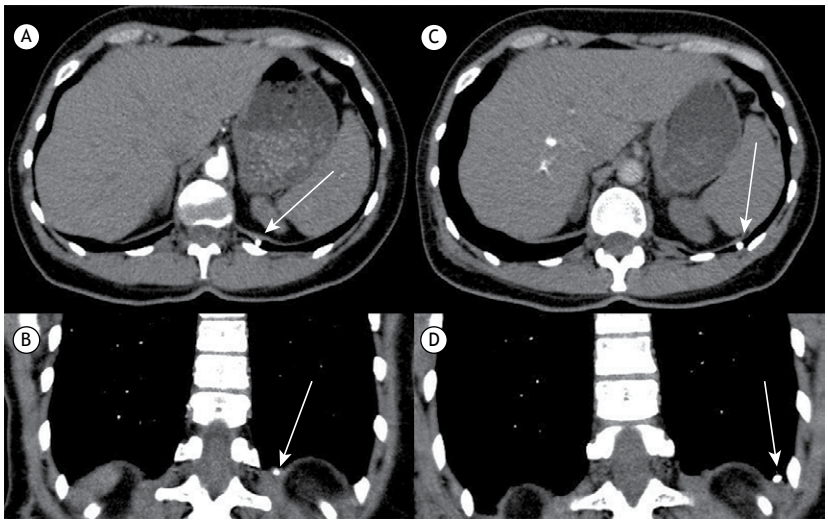

Figure 1. Axial and coronal chest CT scans (A and B respectively), with a mediastinal window setting, showing an 8-mm calcified nodule located medial to the posterior costophrenic angle. Follow-up chest CT scans acquired in the same planes (C and D, respectively), showing that the calcified nodule had migrated laterally.

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