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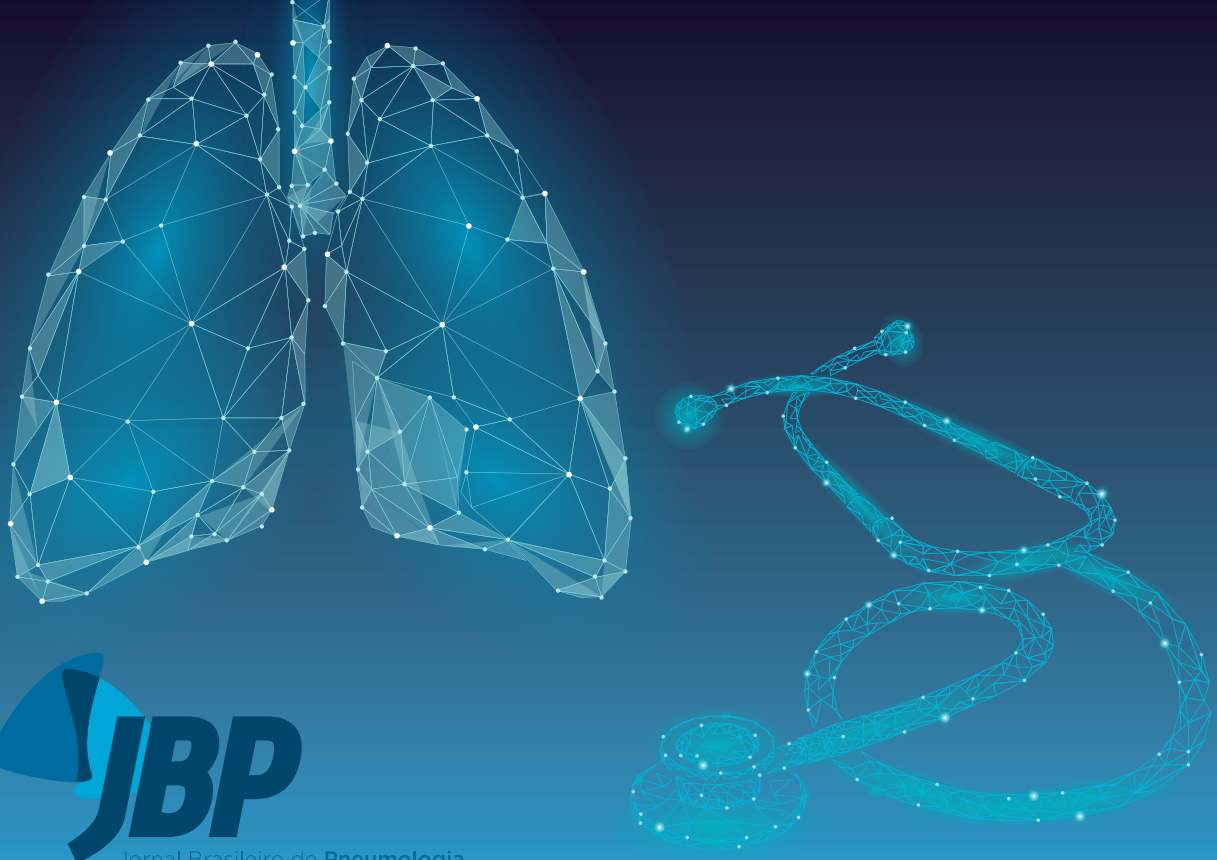
HIGHLIGHT

COPD and the Brazilian Unified Health Care System

Risk of death after pulmonary thromboembolism

Smoking cessation and weight gain



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Jornal Brasileiro de Pneumologia and *Sociedade Brasileira de Pneumologia e Tisiologia*: perspectives for the next four years

Bruno Guedes Baldi[1,2,a], José Miguel Chatkin[3,4,b]

The *Jornal Brasileiro de Pneumologia* (JBP) is the leading journal in the field of respiratory medicine in Latin America. It is well established as a major scientific journal in Brazil, and its international visibility has gradually increased. Recent positive results were made possible by the efforts of JBP editors and reviewers, as well as by the unconditional support of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), which is currently the primary supporter of the JBP. During the period in which the JBP was penalized by Thomson Reuters, the support provided by the SBPT and the hard work of JBP editors and reviewers were essential for the recovery of the Journal.[1]

The primary objectives of the JBP are as follows: to educate and update SBPT members not only on diseases that are highly prevalent (such as tuberculosis, smoking, obstructive lung diseases, and sleep-disordered breathing) but also on those that are rarer[2-5]; to increase the body of knowledge in the field of respiratory diseases and related areas; and to disseminate, strengthen, and contribute to the internationalization of research in Brazil.

According to the World Health Organization, respiratory diseases will be a major cause of morbidity and mortality in the coming years. In this context, it is important that the JBP and the SBPT continue to work together in order to disseminate up-to-date knowledge to SBPT members, thus benefitting patients. Attractive features of the JBP include the following: national and international dissemination of its content, which can be accessed in Portuguese and in English; free submission and publication of articles; and content aimed at pulmonologists and other medical and nonmedical specialists. Updated data from the JBP show that 414 articles were submitted in 2018. Of those, 67% were original articles, and 72% were articles written by researchers in Brazil. Approximately 70% of the articles that are submitted for publication in the JBP are rejected, approximately 120 articles being published each year.

Achievements of past JBP editorial boards include the following: 1) consolidation of the Journal as an international publication, with increases in the impact factor of the JBP, the number of articles submitted by authors from other countries, and collaboration among several groups[6]; 2) increased citations of JBP articles in other journals; 3) creation of the position of Vice Editor of the JBP, a position that allows its occupants to gain experience with the JBP, thus facilitating the continuation of measures taken by the former editorship and the transition from one editorship to another[6]; 4) decentralization of editorial decisions, associate editors having come to play an increasingly important role in the JBP[1,2]; 5) publication of review articles that can be used as reference and have clinical applicability,[1] with a high rate of approval among SBPT members (as noted in a recent survey); 6) creation of the Continuing Education series of articles (on Imaging and Scientific Methodology), also with a high rate of approval among SBPT members; 7) increased rejection rate for articles submitted to the JBP in recent years, reflecting increased stringency in the evaluation of submitted articles and, consequently, increased quality of publications; 8) choice of a different company to manage the JBP site for article submission; and 9) partnerships with other journals, such as the European Respiratory Journal and Pulmonology (previously *Revista Portuguesa de Pneumologia*).

The new editorial board of the JBP comprises the Editor-in-Chief, the Vice Editor, and 19 associate editors (14 in Brazil and 5 elsewhere). In the coming years, the expectation is that the JBP will achieve the following goals: 1) publication of updated guidelines for the management of major respiratory diseases with the support of the SBPT; 2) maintenance of or increase in the impact factor of the JBP; 3) increased submission of quality articles by researchers in Brazil and other countries through collaborative projects; 4) compliance with SciELO proposals for the next five years (such as inclusion of the ORCID iD of all authors; continuous publication of articles, increasing the speed with which they become available online and, consequently, their exposure and citation potential; a board of associate editors on which 20-30% are affiliated with institutions outside the country; and inclusion of a description of each author's contribution in all manuscripts)[7,8]; 5) until the implementation of a continuous publication model, rapid online publication of articles ahead of print[7,9]; 6) optimization of the time from manuscript submission to first response to authors, as well as from manuscript submission to publication; 7) optimization of the JBP website and increased dissemination of the most viewed and most cited articles; 8) use of social media to disseminate the JBP and its most relevant articles; 9) creation of the Continuing Education: Respiratory Physiology series of articles; and 10) expansion of the interface between the JBP and international societies and journals.

One of the major challenges is to encourage reviewers to engage with the articles. It is essential that the role

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of reviewers in evaluating JBP manuscripts be more widely recognized in order to expedite and improve their evaluation, as discussed in a recent editorial.[6] One of the proposals is to invite promising early-career researchers to act as reviewers.

The primary mission of the SBPT is to provide quality continuing education on respiratory medicine using up-to-date scientific and technical resources. The vision of the SBPT is to be recognized for its management excellence, encouraging best practices for quality and safety in patient care and having fully integrated, committed, and satisfied members. To that end, the SBPT has adopted the following as its core values: ethics, respect for life, and a humanistic approach to everything it does, valuing the professional dignity of its members and promoting the best interests of patients and the community.

The new (2019-2020) SBPT board believes that many projects require long-term planning in order to come to fruition. Therefore, the 2019-2020 board will work in conjunction with the next SBPT president, elected to serve a two-year term, beginning in 2021, in order to plan actions that will be evaluated more objectively in four years' time.

Some of the aforementioned proposals include projects initiated during the previous term and new, short- and long-term initiatives, as follows: 1) to encourage member participation in SBPT events and programs—the *ATUALIZAR* (UPDATE) program, a successful initiative that, on the basis of pre-established criteria, sponsored the participation of a significant number of SBPT members in national and international events, will remain in effect, albeit with modifications; 2) to replace at least 30% of lecturers with new lecturers after each SBPT promotion, a committee or group tentatively named SBPT *JOVEM* (YOUNG SBPT) being created to that end; 3) to maintain the autonomy of the JBP and expand its role as a disseminator of research findings; 4) to increase partnerships with international societies in an attempt to promote the exchange of conference lecturers, joint publications with international researchers, internships at quality institutions, problem solving, and the integration of continuing education programs in pulmonology worldwide, as well as to provide education on an ever-increasing number of subspecialties, many of which continue to pose a challenge for pulmonologists in Brazil, including eHealth, robotics, and environmental pollution; 5) to maintain close ties with the Brazilian Federal Medical Council and proceed with the process of qualification for respiratory medicine procedures with the Brazilian Medical Association in order to increase the number of job opportunities for pulmonologists; 6) to maintain the support that the SBPT provides to the training of residents in pulmonology, residents in clinical medicine, and general practitioners in respiratory medicine; 7) to increase the participation of medical and nonmedical professionals in all SBPT events and programs; 8) to maintain a focus on sustainability by seeking alternative sources of funding for the SBPT and the JBP; 9) to maintain a policy of transparency in all SBPT processes and projects; and 10) to work more closely with all 22 state societies of pulmonology.

In summary, the JBP and SBPT have overlapping missions, and the new boards have great responsibilities. Major challenges for the coming years are to continue and improve on what has been achieved by former boards and develop new strategies to achieve excellence in an objective, transparent, and realistic manner.

We would like to thank all of the SBPT members who agreed to be members of the editorial board of the JBP and the SBPT board as of January of 2019. We also count on the indispensable assistance of all 3,800 SBPT members, many of whom are also JBP reviewers.

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Should we use prognostic scores for acute pulmonary thromboembolism in clinical practice?

Marcelo Basso Gazzana[1,2,3,a], Igor Gorski Benedetto[1,2,3,b]

Acute pulmonary thromboembolism (PTE) is a life-threatening disease, the incidence of which has increased in recent years; however, the mortality of acute PTE has decreased, possibly due to improved diagnostic and treatment strategies.[1] In this context, establishing a prognosis is essential for patient management.

Risk stratification has long been used in the management of acute conditions and acute exacerbations of chronic diseases, including myocardial infarction, stroke, and asthma exacerbation. The objectives of stratifying patients into risk groups are as follows: to inform patients about the course of their disease; to identify lower-risk patients who can be discharged early or even receive home treatment (given that novel oral anticoagulants such as apixaban and rivaroxaban do not require a heparin bridge); to identify higher-risk patients requiring treatments that are more aggressive, such as exogenous thrombolysis and embolectomy; to select patients for clinical drug trials; and to compare hospitals by means of severity-adjusted quality health care outcomes.[2]

Hemodynamic instability is the strongest predictor of the outcome of acute PTE. However, most patients are normotensive and constitute a heterogeneous group, other variables being required for risk stratification. Although echocardiographic variables (showing right ventricular dysfunction) and levels of biomarkers (such as troponin and natriuretic peptides, showing myocardial injury or stress) are primarily used in daily practice, the major guidelines on acute PTE recommend that prognostic scores be used after hemodynamic assessment.[3,4] Any new score requires the following: 1) derivation; 2) validation in a different population; and 3) study of its clinical impact.[2]

The Pulmonary Embolism Severity Index (PESI), comprising 11 variables and 5 risk classes (ranging from I to V), and the simplified PESI, comprising 6 variables and 2 risk classes (i.e., low risk and high risk), are among the most widely studied and validated prognostic scores for acute PTE. A PESI risk class of I or II indicates a low-risk population (as does a simplified PESI of zero), the 30-day mortality rate being less than 3%.[5,6] The PESI and the simplified PESI can identify a low-risk population in 45% of patients with acute PTE and reduce the length of hospital stay without the need for additional tests and without increasing the risk of death, recurrent PTE, or severe bleeding. Evaluation is complemented by The Hestia Study criteria for outpatient treatment.[7] In a meta-analysis of 71 studies (a total of 44,298 patients), prognostic scores were shown to be valid and useful for identifying low-risk patients.[8] Therefore, patients can be treated at home safely and efficiently.[3,9]

It should be noted that the PESI has a high negative predictive value but a low positive predictive value.[10] This means that the PESI does not adequately identify high-risk patients among normotensive patients requiring intensive monitoring and, in some cases, treatments that are more aggressive. Other scores are more appropriate for this purpose, including the Bova score (a systemic blood pressure of 90-100 mmHg, elevated troponin levels, right ventricular dysfunction as assessed by echocardiography or CT, and a heart rate ≥ 110 bpm); Prognostic Factors for Pulmonary Embolism, including altered mental status, cardiogenic shock on admission, cancer, serum brain natriuretic peptide (BNP) levels, and right ventricular/left ventricular ratio as assessed by echocardiography; and the Heart-type Fatty Acid-Binding Protein, Syncope, and Tachycardia score. In addition, a clinical prognostic rule should be used in order to predict the risk of intracranial bleeding in patients undergoing thrombolytic therapy, a borderline risk-benefit ratio being taken into account in normotensive patients with right ventricular dysfunction alone.[11] Figure 1 shows a management algorithm based on a risk stratification algorithm presented in a nonsystematic review published recently.[2] It should be noted that this is a practical approach based on independent clinical studies; it has yet to be validated as a viable strategy.

In the current issue of the JBP, Soriano et al.[12] published a single-center study aimed at validating the original and simplified versions of the PESI in a historical cohort of patients in Brazil in order to predict 30-day mortality following acute PTE. The authors retrospectively evaluated 123 patients admitted to the emergency department of a public, tertiary referral hospital that exclusively serves patients requiring acute care. They concluded that the PESI can predict 30-day mortality, the original version being more accurate than the simplified version.

Certain points should be noted. Patients with acute PTE were identified on the basis of International Classification of Diseases, 10th revision (ICD-10) codes on discharge records. However, ICD-10 codes have low sensitivity for identifying patients with acute PTE.[13] Therefore, it is possible that some patients (particularly low-risk patients) were missed and not included in the study, a possibility that might explain the high proportion of patients with cardiogenic shock. It is also of note that the

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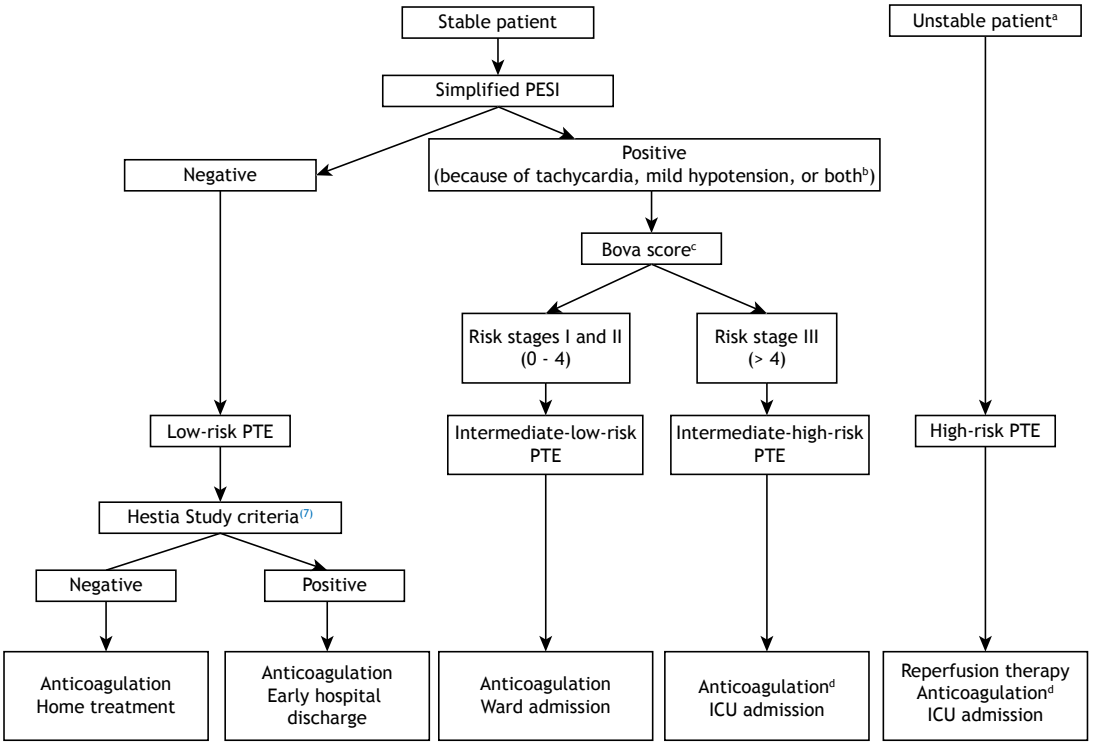

Figure 1. Treatment algorithm based on risk stratification. PESI: Pulmonary Embolism Severity Index; and PTE: pulmonary thromboembolism. [a]Unstable patient: a systemic systolic blood pressure of < 90 mmHg or a 40-mmHg drop lasting longer than 15 min and not caused by new arrhythmias, hypovolemia, or sepsis; or cardiogenic shock (reduced cardiac output associated with signs of tissue hypoperfusion, including oliguria, decreased level of consciousness, decreased skin perfusion, and lactic acidosis). [b]Mild hypotension: a systemic systolic blood pressure of 90-100 mmHg. [c]The Bova score includes the following variables: biomarker (troponin) levels and right ventricular dysfunction as assessed by echocardiography or chest CT angiography. [d]Unfractionated heparin should be the preferred anticoagulation strategy in such cases. Adapted from Morillo et al.[2]

study evaluated patients who had been hospitalized for acute PTE. It did not include patients who had been hospitalized for other reasons and had acute PTE during their hospital stay (a condition known as secondary pulmonary embolism or hospital-acquired pulmonary embolism). This reduces the external validity of the results.

Despite the limitations inherent to studies of historical data conducted at highly specialized centers, the study by Soriano et al.[12] is relevant and provides national data that can bridge the gap between clinical studies and the daily practice of pulmonology in Brazil. In patients with an established diagnosis of acute PTE, it is important to stratify the risk of poor outcome, clinical prognostic scores being useful for this purpose. They are also useful in selecting the most appropriate therapy for a given patient. However, prospective randomized studies focusing on patient management (risk stratification-guided therapy) are needed for external validation of this concept and, consequently, a higher level of evidence to strengthen recommendations for the management of patients with acute PTE in Brazil.

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COPD: more treatment will translate to better breathing. Will it?

Paulo José Zimermann Teixeira[1,2,3,a], Marcelo Ferreira Nogueira[2,3,b]

COPD is the third leading cause of death from a chronic noncommunicable disease in Brazil, and its prevalence varies by region, depending on the prevalence of smoking.[1] The treatment was previously very limited, based on short-acting bronchodilators, xanthines, and inhaled corticosteroids (ICS), as well as oral corticosteroids for very severe cases. However, the treatments have now, after a few years, become more broad and effective. Gaining precise knowledge of the indications, limitations, and potential risks/benefits of each treatment poses a challenge, because it is necessary to modify the simplistic thinking of those who insist on maintaining the ICS for all patients and the passivity of those who do not consider long-acting muscarinic antagonists (LAMAs) an option. The fee schedule of the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System) has not been readjusted for several years, because, in the minds of managers, doctors and hospitals will always solve all of the problems. Therefore, the technicians responsible for the treatment protocols need to know that COPD patients can breathe better after the proposed treatment, despite the fact that there is not always evidence of a reduction in mortality. In fact, there is already a large body of evidence that justifies modifying the way we view and treat COPD patients in public and private clinical practice in Brazil.[2,3]

In this issue of the JBP, Pinto et al.[4] demonstrate, with great elegance, the regrettable state of COPD treatment in the public health care system in Brazil. Theirs was a cross-sectional study involving patients diagnosed, on the basis of the clinical and spirometric findings, with moderate to severe COPD. All of the patients were referred from the SUS-affiliated Bahia State Public Health Care Network to a referral outpatient clinic. The authors demonstrated the reality of the SUS, emphasizing that the approach differs among states,[4] because it depends heavily on the economic condition, although there have been attempts by several state societies to sensitize managers to the need to create treatment protocols for patients with COPD.

Pinto et al.[4] included 383 patients, classified by risk of exacerbation and severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (risk group A, B, C, or D) and the Brazilian National Ministry of Health criteria (moderate, severe, or very severe), respectively. The authors questioned the patients about the use of COPD medications, subsequently assessing the appropriateness of the treatment (to identify undertreatment or overtreatment) in relation to national and international guidelines. The majority of the patients (70.5%) belonged to the highest risk group (GOLD group D), and 48.8% of the patients were in the severe group according to the spirometric criteria. Pinto et al.[4] found that 63.7% of patients in their sample were not treated in accordance with the Brazilian national guidelines (i.e., were treated inappropriately). The authors identified cases of undertreatment in their sample. Only half of the patients were using a long-acting bronchodilator. In addition, although 80% of the patients had a Medical Research Council dyspnea scale score ≥ 2 and 85.1% of the sample had a high risk of exacerbation (GOLD group C or D), in which case the use of a LAMA is definitely indicated, only 9.7% of the sample were using one. In addition, more than half of the undertreated patients were using no medication, perhaps indicating a failure of guidance regarding the importance of continued treatment. A study conducted in the Brazilian state of Santa Catarina and involving 50 hospitalized patients showed that, in relation to the national guidelines, 74% were receiving inappropriate treatment and 38% were being undertreated.[5] Another study, conducted in the state of Rio Grande do Sul,[6] collected data related to 161 patients with COPD who were referred for pulmonary rehabilitation, most of them from the SUS-affiliated outpatient clinics of two institutions.[6] In that study, 51.3% of the patients classified as being in GOLD group A were receiving an ICS unnecessarily and only 35.2% of those classified as being in GOLD group D were receiving a long-acting β_2 agonist (LABA) combined with a LAMA and an ICS (LABA+LAMA+ICS), whereas 82.1% and 95.2% of those classified as being in GOLD groups C and D, respectively, were receiving treatment that was in agreement with the GOLD recommendations.

In the Pinto et al. study,[4] overtreatment (represented by the overuse of ICS) was significantly more common in patients with moderate COPD and in those at a lower risk of exacerbation, being identified in more than half of the individuals in the GOLD A and B groups (54.5% and 54.3%, respectively), as well as in 46.2% of the patients with moderate COPD. In addition to the underuse of long-acting bronchodilators and the overuse of ICS, as were quite well demonstrated by the authors, factors such as a low level of education, low income, not using oxygen therapy, and not having received the influenza vaccination have also been associated with inappropriate treatment of COPD.[5]

The current recommendation for COPD treatment is based on an accurate diagnosis and on phenotypic

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characteristics, especially whether or not the patient is a frequent exacerbator. In a recent review,[3] it was recommended that, in patients with severe dyspnea and a low risk of exacerbation, dual bronchodilator treatment (LABA+LAMA) is indicated. A recent meta-analysis showed that the use of the LABA+LAMA+ICS combination reduced the risk of exacerbation (RR = 0.70; 95% CI: 0.53-0.94) and improved FEV_1 (mean increase, 37.94 mL; 95% CI: 18.83-53.89) when compared with the use of the LABA+LAMA combination.[7] However, triple therapy was found to have a protective effect mainly in the patients who had an eosinophil count ≥ 300 cells/μL (RR = 0.57; 95% CI: 0.48-0.68). In that same meta-analysis,[7] the authors concluded that patients on long-term bronchodilator therapy or using the LABA+LAMA combination who continue to experience exacerbations and have an eosinophil count ≥ 300 cells/μL would benefit from the triple therapy (LABA+LAMA+ICS). The risk of pneumonia was not found to be higher among the patients on triple therapy than among those on monotherapy or dual therapy.

Now that we have the new combinations of LABA+LAMA and LABA+LAMA+ICS, tailoring the treatment will be of fundamental importance. It is always important to emphasize that the pharmacological treatment of COPD should be complemented by measures such as smoking cessation, encouraging physical activity, pulmonary rehabilitation, and vaccination.[3] However, all of the new evidence that is being unveiled will have no value if the knowledge is not disseminated. We cannot risk having primary care physicians who think that every wheezing patient has asthma and that there is no justification for performing spirometry (because the only treatment option is LABA+ICS) and who believe that (because LAMA has been approved for asthma) prescribing LABA+LAMA+ICS will resolve everything. We want to avoid the phenomenon in the pattern of prescribing treatment for COPD that occurred in the United Kingdom, in which all of the patients were moved from LABA+ICS to LABA+LAMA+ICS,[8] a change that should not be made without clear, well-defined criteria. In conclusion, although undertreatment can worsen breathing, overtreatment will not necessarily improve breathing.

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Hyperinflation surrounding a solitary nodule

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

A 28-year-old asymptomatic woman had a chest X-ray as part of the preoperative workup for breast aesthetic surgery. The chest X-ray showed a nodular density in the right lower lobe, a finding that was confirmed by CT.

The detection of a solitary pulmonary nodule on imaging is worrisome because one of its most common etiologies is bronchogenic carcinoma. Therefore, in the initial assessment of such a nodule, it is essential to determine whether it meets the imaging criteria for benignity. The CT scan showed a lobulated nodule surrounded by an area of hyperinflation (Figure 1A). The image acquired during expiration more clearly showed the area of air trapping (Figure 1B). In the case reported here, the key to the diagnosis is the area of air trapping that surrounded the nodule. This finding is highly suggestive of bronchial atresia.

Bronchial atresia is an uncommon congenital anomaly, characterized by interruption of a bronchus with mucus accumulation in the distal bronchial stump (mucocele or bronchocele). This change is accompanied by hyperinflation of the lung parenchyma of the obstructed segment, as a result of collateral ventilation through pores of Kohn, channels of Lambert, and interbronchiolar channels.[1] Bronchial atresia is a benign condition that is usually asymptomatic and is often diagnosed incidentally. In asymptomatic cases, surgery is not indicated. The approach is conservative. Some patients can have recurrent infections, in which case surgical resection should be considered.

The differential diagnosis of bronchial atresia includes other congenital diseases that can result in areas of decreased lung parenchymal density, such as cystic adenomatoid malformations, pulmonary sequestration, congenital lung cysts, and congenital lobar emphysema.[2] In the first three, well-defined walls usually separate the hypodense area from the surrounding normal parenchyma. Although hyperinflation due to lobar emphysema can be very similar to that due to bronchial atresia, the absence of mucocele establishes the differential diagnosis. It is important to note that most of the etiologies seen in children, even congenital ones, can also be seen in adults, because these anomalies usually have a benign course, patients often remaining asymptomatic into adulthood. Although the mucocele had a nodular appearance in the case reported here, it often has an oval or branching tubular appearance. In such cases, the differential diagnosis includes other abnormalities that cause mucoid impaction, such as allergic bronchopulmonary aspergillosis and cystic fibrosis, as well as vascular malformations. However, those conditions are not associated with hyperinflation of the surrounding parenchyma. In summary, the finding of a nodular, oval, or branching tubular lesion with hyperinflation of the surrounding lung parenchyma is highly suggestive of bronchial atresia.

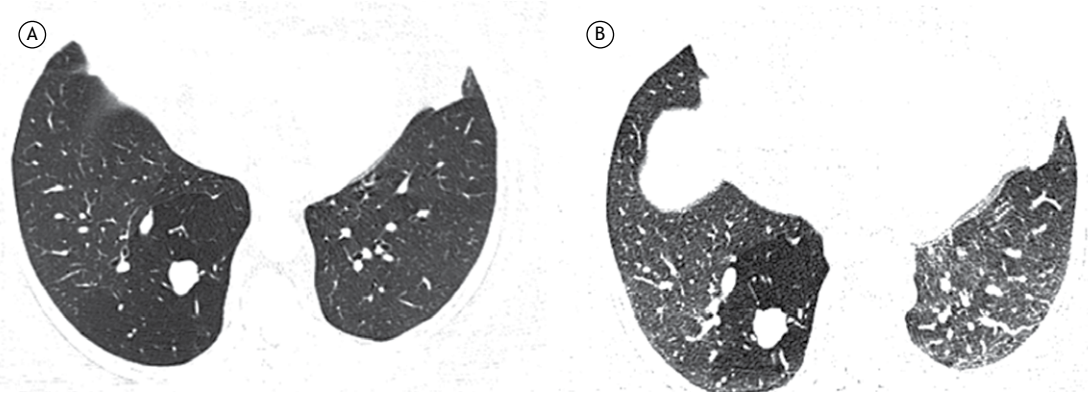

Figure 1. Axial CT scans of the chest, with lung window settings, at the level of the lung bases, acquired during inspiration (in A) and expiration (in B), showing a lobulated nodule in the posterior basal segment of the right lower lobe, with surrounding hyperinflation (air trapping), which is seen more clearly in the image acquired during expiration (in B).

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Writing an effective response to reviewers: the goal is to improve the study and get it published!

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PRACTICAL SCENARIO

We are very excited because a group of students from the Latin-American Methods in Epidemiologic, Clinical, and Operations Research (MECOR) program submitted a manuscript to an international journal and received a response stating that the manuscript is of interest but, based on the reviewers' comments, "major revisions are required". The students have contacted us because this is their first manuscript and they want to make sure that they respond to the reviewers effectively.

HOW TO STRATEGICALLY RESPOND TO REVIEWERS

As directors of the Latin-American MECOR program, we instill in our students to approach clinical research using sound methods from idea to publication. We provide many resources and guidelines related to research methodology, writing protocols, manuals of procedures, and original manuscripts. Here we provide a summary of recommendations, based on published literature[1,2] and our own experience, for responding to reviewer comments when a journal invites authors to resubmit.

First, we recommend that authors carefully read all of the comments made by the reviewers and distinguish between those that are positive and those in which the reviewers are criticizing or requesting revisions. It is very important to determine whether the comments can be adequately addressed and meet the expectations of the reviewers. Second, we strongly emphasize the need to quickly overcome feelings of frustration, sadness, and even a sense of unfairness. Remember that the article has not been rejected and the editor is giving you the opportunity to revise and resubmit; therefore, you need to get organized and respond to each comment carefully and politely, even when you do not agree with the reviewer (Table 1). Try to approach this effort with a positive attitude and use the comments made by the reviewers to your advantage. It is essential to prioritize the comments and make sure that the most important ones (those in which the reviewers request major changes) are addressed appropriately. For those who are new to this process, we highly recommend working with someone who has experience in responding to reviewers to help in this prioritization process. Third, when you resubmit your revised manuscript to the journal, the goal is to show the editor and reviewers that you have taken this process seriously by addressing every comment in detail and making all necessary changes. It is crucial that you communicate these revisions effectively through clear, simple, and straightforward language. If the authors are not native speakers of the language in which the journal is published (e.g., English), it is imperative that the final version of the response to reviewers be evaluated by an expert translator or editor.

In summary, an important goal of clinical researchers is to publish their work in peer-reviewed journals as a means of improving human health. That involves going through the peer review process and responding to the reviewer comments in an effective manner. We encourage all researchers who are starting to engage in publishing their work to develop a systematic approach when responding to reviewers. The process can be frustrating and tedious, but, in the end . . . the goal is to improve your manuscript and get it published!

Table 1. Process to successfully respond effectively to peer reviewer comments.

Task	Action 1	Action 2	Goals
Create a Word document into which you copy and paste each reviewer comment separately. Number the comments and label them according to the reviewer (e.g., Rev. 1 Comment 1).	Discuss each comment with your team and come to consensus on how to respond. You may agree or disagree with a given reviewer's comment, but you will need to politely respond to all comments.	Answer each comment separately, place them directly below the reviewer's comment (make sure there are no grammatical mistakes or misspellings), and make the corresponding changes in the revised manuscript.	This process shows the editor and the reviewers that you are dedicated and have taken the review seriously; and that you have made it easy for them to re-evaluate your manuscript.

Final products: 1. A letter to the editor in which the authors thank the editor for the opportunity to revise the paper and a list of all reviewer comments with the authors' responses; 2. A revised manuscript including all of the changes that have been made, which should be identified through the use of a different font, a different color, or *italicization*.

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Management of COPD within the Brazilian Unified Health Care System in the state of Bahia: an analysis of real-life medication use patterns

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Study carried out in the Serviço de Pneumologia do Complexo Hospitalar Universitário Professor Edgard Santos, Universidade Federal da Bahia, Salvador (BA) Brasil.

ABSTRACT

Objective: To describe COPD pharmacological treatment patterns in the state of Bahia, Brazil, and to evaluate the extent to which these patterns conform to clinical guidelines for the management of COPD. **Methods:** This was a cross-sectional study of 441 patients referred from the Public Health Care Network of the state of Bahia to a public referral outpatient clinic of a COPD management program of the Brazilian Unified Health Care System. Individuals with a spirometry-confirmed diagnosis of moderate to very severe COPD were included in the study. Patients were evaluated as to whether they had used any COPD medications in the last seven days. The appropriateness or inappropriateness (undertreatment or overtreatment) of the patient's pharmacological treatment was evaluated by comparing the patient's current treatment with that recommended by national and international guidelines. **Results:** A total of 383 individuals were included in the analysis. Approximately half of the patients (49.1%) used long-acting bronchodilators. These patients were older and had had the disease longer. Of the sample as a whole, 63.7% and 83.0% did not receive pharmacological treatment in accordance with international and national recommendations, respectively. Inappropriateness due to undertreatment was indentified in more than half of the patients. **Conclusions:** Long-acting bronchodilators are frequently underused in individuals with moderate to very severe COPD within the Brazilian Unified Health Care System in the state of Bahia. Most patients in our sample were treated inappropriately, and undertreatment predominated. Strategies to improve access to long-acting bronchodilators and the quality of COPD pharmacological management are required.

Keywords: Pulmonary disease, chronic obstructive/therapy; Drug therapy; Clinical protocols

INTRODUCTION

COPD is an important cause of morbidity and mortality worldwide. Low- and middle-income countries such as Brazil account for more than 90% of all deaths.[1,2] Despite its significant economic, personal, and social impact, COPD remains underdiagnosed and undertreated, especially in these countries, because of obstacles posed by health care systems to its diagnosis and because of limited access to medications that are essential for treating respiratory diseases.[3-7]

It is known that the management of a large number of COPD patients can be improved by developing and implementing evidence-based treatment guidelines.[8] However, despite the existence of such guidelines, several studies have shown important gaps between guideline recommendations and clinical practice.[9-11] Recently, a study conducted in primary care settings in four countries in Latin America showed that approximately 60% of the patients diagnosed with COPD and 10% of the individuals with a previous diagnosis of COPD

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did not use bronchodilators.[7] In Brazil, one study estimated that 83.3% of the patients diagnosed with COPD had not used any medications to treat the disease in the previous 12 months.[12] An analysis[11] of prior treatment of hospitalized patients with COPD revealed that approximately half of them did not use maintenance treatment in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations.[1]

Despite the high burden of COPD in Brazil, to date there has been little evidence on the level of appropriateness of COPD treatment in the country, especially from the perspective of the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System). Data from our study may be useful in planning initiatives to improve the quality of management of this disease.[13]

The objective of the present study was to describe COPD pharmacological treatment patterns in a population of patients treated within the SUS in the state of Bahia, Brazil, and to investigate the extent to which these patterns conform to clinical guidelines for the management of COPD.

METHODS

This was a cross-sectional study of patients previously diagnosed with COPD who were referred from the *Rede de Atenção à Saúde* (RAS, Public Health Care Network) of the SUS in the state of Bahia to the Referral Outpatient Clinic of a public COPD management program (*Programa Respira Bahia* [Breathe, Bahia Program]) of the Octávio Mangabeira Specialized Hospital, located in the city of Salvador, Brazil. The program is an initiative of the Bahia State Health Department in partnership with the Department of Pulmonology of the Federal University of Bahia Professor Edgard Santos University Hospital, located in that same city, aimed at implementing a network of care for patients with respiratory symptoms in the state of Bahia to improve the quality of clinical management of and the health care system's decision-making ability regarding respiratory diseases (tuberculosis, COPD, asthma, acute respiratory infection, and lung cancer). The program activities for COPD include medical and pharmaceutical care, with free continued dispensation of medications, which are made available by the Pharmacy Department of the Referral Outpatient Clinic. The medications provided by the program included the following: short-acting β_2 agonists (SABAs); and long-acting bronchodilators—long-acting muscarinic antagonists (LAMAs) or long-acting β_2 agonists (LABAs), alone or combined with inhaled corticosteroids (ICSs). The medications were prescribed by pulmonologists involved with the program, in accordance with a COPD patient treatment protocol established by the Bahia State Health Department on the basis of the 2010 GOLD treatment recommendations.[14]

The inclusion criteria were as follows: being a COPD patient aged ≥ 40 years; being enrolled in the Breathe, Bahia Program between June 2011 and January 2012; having GOLD II (moderate), GOLD III (severe), or GOLD IV (very severe) COPD[14]; and having a post-bronchodilator FEV_1/FVC ratio < 0.7 and a post-bronchodilator FEV_1 < 80% of predicted, as measured by spirometry. The exclusion criteria were as follows: having asthma; declining to participate in the study; and being unable to give written informed consent.

Data were collected through interviews conducted by two pharmacists and a pulmonologist, all of whom had been previously trained, during enrollment in the program. To that end, they used a structured questionnaire addressing the following: demographic variables—age, gender, and self-reported race; socioeconomic variables—number of years of schooling and per capita family income (in number of times the national minimum wage); and clinical variables—smoking status, smoking history, number of comorbidities, COPD duration (in years), spirometry results (pre- and post-bronchodilator FEV_1), baseline dyspnea, COPD spirometric severity (moderate, severe, and very severe) based on the degree of airflow limitation, and COPD classification (risks and symptoms) into GOLD groups (A, B, C, and D).[14] Patients were asked whether they had used any COPD medications in the past seven days. COPD medications were stratified into four classes: short-acting bronchodilators—short-acting muscarinic antagonists (SAMAs), SABAs, and their combinations; long-acting bronchodilators (LAMAs and LABAs, alone or combined with ICSs); ICSs; and methylxanthines.

Patients were classified as GOLD group A (low risk and fewer symptoms), B (low risk and more symptoms), C (high risk and fewer symptoms), or D (high risk and more symptoms).[1] In addition, participants were classified as having moderate, severe, or very severe COPD, in accordance with the guidelines of the Brazilian National Ministry of Health Department of Health Policies.[15]

The appropriateness or inappropriateness (undertreatment or overtreatment) of the patient's pharmacological treatment was evaluated by comparing the patient's current treatment with that recommended by international and national guidelines.[1,15] For both guidelines, undertreatment was defined as the complete absence of pharmacological treatment or the lack of use of recommended medications. On the basis of national guidelines,[15] overtreatment was defined as the use of ICSs in patients with moderate COPD or the use of ICSs + long-acting bronchodilators in patients with severe to very severe COPD without recurrent exacerbations. In accordance with international guidelines,[1] overtreatment was defined as the use of ICS + SABA or SAMA or SABA + SAMA in patients classified as GOLD group A, the use of ICS + LABA or LAMA or LABA + LAMA in patients in GOLD group B, or the use of ICS + LAMA or LABA + LAMA in patients in GOLD group C. The sum of the proportions of undertreatment and overtreatment resulted in the proportion of inappropriate treatment.

A COPD exacerbation was defined as an acute-onset change in baseline dyspnea, cough, and/or expectoration that is beyond normal day-to-day variations and can lead to a change in medication.[14]

Baseline dyspnea was assessed with the modified Medical Research Council (mMRC) scale,[16] and symptom presence and absence were defined as scores ≥ 2 and scores < 2, respectively.

Spirometry was performed with a Koko Pneumotach spirometer (PDS Instrumentation Inc., Louisville, CO, USA) that was previously calibrated in accordance with the criteria recommended by the American Thoracic Society/European Respiratory Society.[17] All spirometric variables were expressed as a percentage of predicted normal values for a Brazilian reference population.[18]

Data analysis was performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Data were presented as mean and standard deviation or as frequency and proportion. Differences in demographic, socioeconomic, and clinical variables between patients who used long-acting bronchodilators and those who did not were analyzed by the chi-square test or the Student's t-test. The level of significance was set at $p < 0.05$. Medication use patterns were analyzed by GOLD group, spirometric disease severity, and mMRC dyspnea grade, with the use of the chi-square test. The chi-square test was also used to identify differences in the frequency of appropriate treatment, undertreatment, and overtreatment across spirometric disease severity categories and across GOLD groups.

The study protocol was approved by the Research Ethics Committee of the Bahia State Health Department (Protocol no. 17268313.8.0000.5030). All participating patients gave written informed consent.

RESULTS

A total of 441 patients were recruited for the study. Of those, 383 met the study's inclusion criteria and participated in the analysis (Figure 1). Most patients (65%) resided in the city of Salvador; the rest resided in one of 40 municipalities in the state of Bahia. Of the sample as a whole, 271 patients (70.8%) used COPD medications, approximately half of whom (49.1%) used long-acting bronchodilators.

Most patients were male (67.9%), had a mean age of 65.9 ± 11.1 years, self-reported being non-White (92.7%), and had a family income ≤ one time the national minimum wage (79.6%). Approximately 80% of the patients were symptomatic (mMRC scale scores ≥ 2). Classification of COPD severity based on the degree of airflow limitation was as follows: moderate, in 24.3%; severe, in 48.8%; and very severe, in 26.9%. Most patients were classified as GOLD group C or D (14.6% and 70.5%, respectively), which are groups at higher risk of exacerbation.

Patient general characteristics by long-acting bronchodilator use status (use vs. non-use) are presented in Table 1. Individuals who used long-acting bronchodilators were significantly older and had had the disease longer.

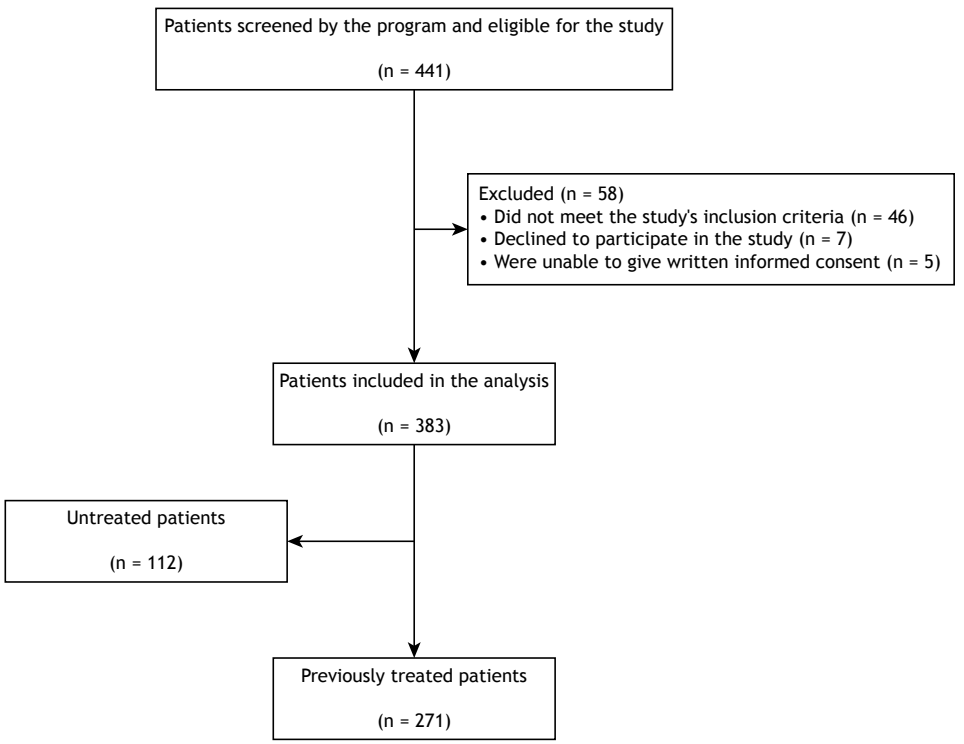

Figure 1. Flow chart of the patients in the study.

The most commonly consumed medications were LABA, in 47.5% of the patients; ICSs, in 44.9%; SABA, in 33.7%; SAMA, in 9.7%; LAMA, in 9.7%; and methylxanthines, in 9.4%. We did not identify significant differences in medication use patterns across the spirometric disease severity levels or GOLD groups (Table 2). However, for those who used SABA, consumption was higher in GOLD groups C and D than in GOLD groups A and B (p = 0.04). In addition, symptomatic patients more commonly used LAMA alone or in combination with LABA or with LABA + ICS.

An assessment of the observed patterns of medication use relative to international and national recommendations[1,15] revealed that only 139 (36.3%) and 65 (17.0%) of the patients received appropriate pharmacological treatment, respectively. According to those guidelines,[1,15] the most common cause of inappropriate treatment was undertreatment, in 55.1% and 53.0% of the patients, respectively. The proportions of appropriately treated, undertreated, and overtreated patients by disease severity (based on the degree of airflow obstruction) and by GOLD group (A-D) are presented in Figures 2 and 3, respectively. The proportion of appropriately treated individuals was significantly higher among patients with severe COPD (22.5%) than among those with moderate or very severe COPD (5.4% and 17.5%, respectively; p < 0.001). Overtreatment was significantly more common in patients with moderate COPD (46.2%) than in those with severe COPD (23.5%) or very severe

Table 1. Patient general characteristics by long-acting bronchodilator use status.[a]

Variable	Any LABD use		p*
	No	Yes	
Gender			
Male	127 (48.8)	133 (51.2)	0.239
Female	68 (55.3)	55 (44.7)	
Age, years	64.1 ± 11.4	67.8 ± 10.4	0.001
Self-reported race			
White	17 (60.7)	11 (39.3)	0.281
Non-White	178 (50.1)	177 (49.9)	
Schooling, years			
< 9	160 (52.1)	147 (47.9)	0.344
≥ 9	35 (46.1)	41 (53.9)	
Per capita family income, number of times the NMW			
≤ 1	160 (52.5)	145 (47.5)	0.232
> 1	35 (44.9)	43 (55.1)	
Smoking history, pack-years	42.6 ± 34.9	39.4 ± 34.5	0.374
Smoking status			
Never smoker	7 (50.0)	7 (50.0)	
Former smoker	173 (50.7)	168 (49.3)	0.957
Smoker	15 (53.6)	13 (46.4)	
COPD duration, years	8.7 ± 8.3	11.0 ± 10.6	0.045
Number of comorbidities			
< 5	185 (51.7)	173 (48.3)	0.259
≥ 5	10 (40.0)	15 (60.0)	
Pre-bronchodilator FEV_1, % predicted	36.51 ± 12.26	36.87 ± 13.47	0.826
Post-bronchodilator FEV_1, % predicted	39.44 ± 13.73	40.32 ± 13.96	0.623
mMRC dyspnea grade			
< 2	42 (53.8)	36 (46.2)	0.562
≥ 2	153 (50.2)	152 (49.8)	
Spirometric severity			
Moderate	45 (48.4)	48 (51.6)	
Severe	97 (51.9)	90 (48.1)	0.853
Very severe	53 (51.5)	50 (48.5)	
GOLD group			
A	11 (50.0)	11 (50.0)	
B	12 (34.3)	23 (65.7)	0.212
C	31 (55.4)	25 (44.6)	
D	141 (52.2)	129 (47.8)	

LABD: long-acting bronchodilator; NMW: national minimum wage; mMRC: modified Medical Research Council; and GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Values expressed as n (%) or as mean ± SD. *Student's t-test or chi-square test.

COPD (27.2%; p < 0.001).GOLD groups C and D had a significantly higher proportion of appropriately treated COPD patients than did GOLD groups A and B (p < 0.001). The proportion of overtreated COPD patients was significantly higher in the lower-risk GOLD groups (A, 54.5%; and B, 54.3%) than in the higher-risk GOLD groups (C, 3.6%; and D, 0.0%; p < 0.001).

DISCUSSION

The present study has shown that 83.0% and 63.7% of the patients in our sample were treated inappropriately according to the recommendations of international and national guidelines,[1,15] respectively. To our knowledge, this is the first large-scale study in Brazil, conducted within the SUS, evaluating the level of appropriateness of COPD pharmacological treatment relative to the recommendations of treatment guidelines. In general, the level of treatment inappropriateness identified in the present study was higher than that observed in other studies conducted in different countries, which found values ranging from 26.0% to 81.3%.[9-11,19-21] This suggests differences in COPD treatment across countries and reveals that there are important gaps between the recommended treatment and the treatment provided to COPD patients within the SUS. However, comparison of results should be made with caution because of the disease severity profile of the patients involved in these studies, most of whom had moderate COPD. In addition, it should be noted that the data presented here were obtained in the setting of the SUS RAS; therefore, the data involved individuals referred from primary, secondary, and tertiary health care settings, unlike most previous studies, which were conducted at referral outpatient clinics. The high level of treatment inappropriateness observed in our study was greater than that previously reported by Giacomelli et al.[11] in a study conducted in Brazil that analyzed the appropriateness of pharmacological maintenance treatment in 50 COPD patients prior to their hospitalization. The authors showed that, relative

Table 2. Distribution of COPD medication use patterns by dyspnea grade. spirometric disease severity. and Global Initiative for Chronic Obstructive Lung Disease (GOLD) group.[a]

Variable	Any SABA use	Any SAMA use	Any LABA use	Any LAMA use	Any ICS use	Any methylxanthine use	Any LABA + ICS use	Any LABA + LAMA use	Any LABA + LAMA + CI use
mMRC dyspnea grade	p = 0.733	p = 0.818	p = 0.787	p = 0.017	p = 0.605	p = 0.311	p = 0.683	p = 0.038	p = 0.045
< 2	32.1	9	42.6	2.6	42.3	6.4	39.7	2.6	2.6
≥ 2	24.1	9.8	47.9	11.5	45.6	10.2	42.3	9.8	9.5
COPD severity	p = 0.071	p = 0.170	p = 0.655	p = 0.493	p = 0.429	p = 0.075	p = 0.599	p = 0.545	p = 0.697
Moderate	24.7	5.4	51.6	8.6	80.5	9.7	46.2	8.6	8.6
Severe	38.5	12.3	46.5	8.6	43.9	6.4	40.6	7.0	7.0
Very severe	33	8.7	45.6	12.6	41.7	14.6	39.8	10.7	9.7
GOLD group	p = 0.040	p = 0.302	p = 0.151	p = 0.117	p = 0.117	p = 0.585	p = 0.281	p = 0.196	p = 0.213
A	13.6	0	50	0	59.1	4.5	50	0.0	0.0
B	20	5.7	65.7	11.4	57.1	14.3	54.3	11.4	11.4
C	39.3	12.5	44.6	3.6	35.7	7.1	35.7	3.6	3.6
D	35.9	10.4	45.6	11.5	44.1	9.1	40.7	9.6	9.3

mMRC: modified Medical Research Council; SABA: short-acting β_2 agonist; SAMA: short-acting muscarinic antagonist; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; and ICS: inhaled corticosteroid. [a]Values expressed as n (%).

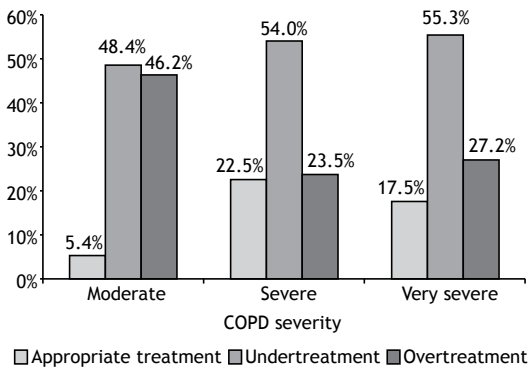

Figure 2. Distribution of individuals appropriately treated, undertreated, or overtreated for COPD, by disease severity as defined by national guidelines.[15]

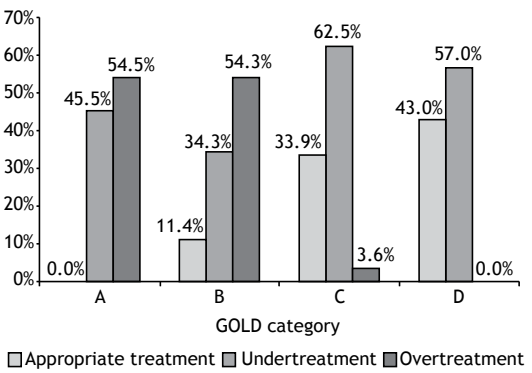

Figure 3. Distribution of individuals appropriately treated, undertreated, or overtreated for COPD, by Global Initiative for Chronic Obstructive Lung Disease (GOLD) category.[1]

to what is recommended by the same international and national guidelines,[1,15] treatment was inappropriate in 50% and 74% of the patients, respectively. Our findings are a cause for concern, given that COPD is a highly prevalent disease with a substantial economic impact on the Brazilian health care system. In addition, lack of compliance with treatment guidelines for COPD is known to be associated with higher total health care costs.[22]

In Brazil, factors such as a low level of education, low income, non-use of oxygen therapy, and lack of influenza vaccination have been associated with inappropriate COPD treatment.[11] Other factors that should be taken into account include low adherence to treatment guidelines for COPD and poor physician knowledge of these guidelines. A survey conducted in 2013 in 12 countries, including Brazil, revealed that there are gaps in the application of treatment guidelines for COPD by physicians in Brazil.[23] An international survey involving some countries showed that 34% of general practitioners in Brazil did not use treatment guidelines for COPD for the management of their patients.[24] In addition, other barriers, such as limited access to health care and medications within the SUS, may be considered.[25]

Long-acting bronchodilators are guideline recommended for the management of symptomatic patients with COPD.[1,26] The benefits of these medications on quality of life, dyspnea, exacerbations, and lung function are well documented in the literature.[26] However, as in our study, evidence has shown that long-acting bronchodilators have been underused in clinical practice in different countries and settings.[11,27-29] We found that approximately half of the patients used long-acting bronchodilators, with consumption being higher in individuals who were older and who had had the disease longer. This value is lower than that found in two recent studies, one conducted in Brazil and one conducted in primary care in the United Kingdom, in which the reported proportion of use of these medications was 64% and 77%, respectively.[11,28] However, it was higher than that found in a multinational, non-interventional study that evaluated bronchodilator use among COPD patients recruited from primary care settings in four countries in Latin America (Argentina, Colombia, Venezuela, and Uruguay).[29] The authors showed that only 30.9% of the patients who had been previously diagnosed with the disease used long-acting bronchodilators, 9.8% of whom as monotherapy and 21.1% of whom as combination therapy with an ICS.

The present study showed that, relative to the GOLD guidelines,[1] 211 patients (55.1%) were undertreated. Of those, 112 (53.1%) did not use any medications to treat the disease. This value contrasts with that reported by a study conducted in Brazil in which inappropriateness due to undertreatment was estimated to be 38%.[11] In another study, Nascimento et al.[12] showed that 50% of the patients who had been previously diagnosed with COPD received some pharmacological treatment for the disease. This observed difference can be explained by the different settings and, especially, by the eligibility criteria and patient recruitment strategies used in the different studies.

It should be noted that access to medications to treat chronic diseases within the SUS varies across the different regions of Brazil.[30,31] In addition, an analysis of data from the Brazilian National Survey on Access to, Use of, and Promotion of Rational Use of Medications, conducted between 2013 and 2014, revealed a high rate of patients' purchase of medications that act on the respiratory system, such as agents against obstructive airway diaseses, with their own resources, suggesting that barriers to cost-free access to this group of medications have yet to be overcome.[31] Furthermore, it is known that medications such as LAMAs are not available within the SUS, with access to them being restricted to states that have their own policies regarding the funding of these medications, such as the state of São Paulo.[32,33] Therefore, we cannot rule out the hypothesis that, for states with limited access to LAMAs, undertreatment is even higher.

Overtreatment as a result of inappropriate ICS use was identified in more than half of the individuals in GOLD groups A and B (in 54.5% and 54.3%, respectively), as well as in 46.2% of the patients with moderate COPD. Although ICS use is limited to specific indications, ICSs have been widely prescribed in clinical practice to individuals who are unlikely to benefit from their use.[9,10,28,34] Another concern related to ICS use in COPD is safety issues, especially because the use of these medications is associated with an increased risk of pneumonia.[35] Recently, some researchers reviewing data from large clinical trials have recommended withdrawal of ICSs from the treatment regimen of patients for whom these medications are not indicated, with maintenance of appropriate bronchodilator therapy.[36] It is likely that the frequency of overtreatment among individuals classified as GOLD A reported here is underestimated, since the study's inclusion criteria, which restricted the sample to patients with moderate to very severe COPD, favored the selection of a limited sample in terms of the proportion of GOLD A patients.

The present study has some limitations that should be considered in the interpretation of our results. The major limitation of this study was that the patients were not randomly selected, generating a potential selection bias. Therefore, we cannot rule out the hypothesis that the patients evaluated do not represent the whole population of COPD patients commonly treated within the RAS in the state of Bahia. However, our results reflect a more heterogeneous real-world population, representative of clinical practice. In addition, we cannot disregard the possibility that our findings do not reflect the current status of COPD treatment in Brazil, since, in 2013, the Brazilian National Ministry of Health established a dedicated clinical protocol and dedicated treatment guidelines for COPD,[32] thus enabling new medications to be incorporated into and dispensed at no charge within the SUS. However, our findings can

be used as historical control for future studies that will enable the monitoring of access to and use of COPD medications in clinical practice.

There is a need for studies evaluating the factors associated with inappropriate COPD treatment and the barriers to physician adherence to treatment guidelines for COPD in clinical practice within the SUS. In addition, further studies are needed to evaluate the impact of the implementation of the clinical protocol and treatment guidelines for COPD[32] mentioned above on the quality of COPD management within the SUS in different settings.

In conclusion, we found that long-acting bronchodilators are frequently underused for the treatment of COPD within the SUS in the state of Bahia. Furthermore, we observed a high frequency of inappropriate treatment, especially undertreatment, revealing important gaps between guideline recommendations for COPD management and clinical practice. Therefore, it is necessary to implement strategies for dissemination of treatment guidelines for COPD among physicians working within the RAS. However, COPD management programs based on multidisciplinary care and free continued access to maintenance treatment can be considered as an alternative for improving the quality of COPD management within the SUS.

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Validation of the Pulmonary Embolism Severity Index for risk stratification after acute pulmonary embolism in a cohort of patients in Brazil

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ABSTRACT

Objective: To validate the Pulmonary Embolism Severity Index (PESI), which was developed for risk stratification after acute pulmonary embolism (PE), for use in Brazil. **Methods:** This was a single-center retrospective study involving patients admitted to the emergency department with acute PE. The original and simplified versions of the PESI were calculated using hospital admission data from medical records. The outcome measure was the overall 30-day mortality rate. **Results:** We included 123 patients. The mean age was 57 ± 17 years, and there was a predominance of females, who accounted for 60% of the cohort. There were 28 deaths, translating to an overall 30-day mortality rate of 23%. In the cluster analysis by risk class, overall 30-day mortality was 2.40% for classes I-II, compared with 20.00% for classes III-IV-V (relative risk [RR] = 5.9; 95% CI: 1.88-18.51; p = 0.0002). When we calculated overall 30-day mortality using the simplified version (0 points vs. ≥ 1 point), we found it to be 3.25% for 0 points and 19.51% for ≥ 1 point (RR = 2.38; 95% CI: 0.89-6.38; p = 0.06). Using the original version, a survival analysis showed that risk classes I and II presented similar Kaplan-Meier curves (p = 0.59), as did risk classes III, IV, and V (p = 0.25). However, the curve of the clusters based on the original version, showed significantly higher mortality in the III-IV-V classes than in the I-II classes (RR = 7.63; 95% CI: 2.29-25.21; p = 0.0001). The cluster analysis based on the original version showed a greater area under the ROC curve than did the analysis based on the simplified version (0.70; 95% CI: 0.62-0.77 vs. 0.60; 95% CI: 0.51-0.67; p = 0.05). **Conclusions:** The PESI adequately predicted the prognosis after acute PE in this sample of the population of Brazil. The cluster analysis based on the original version is the most appropriate analysis in this setting.

Keywords: Pulmonary embolism; Severity of illness index; Risk assessment.

INTRODUCTION

Acute pulmonary embolism (PE) is a prevalent disease with a broad spectrum of clinical presentation, ranging from asymptomatic (an incidental finding on CT) to severe hemodynamic instability and sudden death.[1] In this diverse scenario, some tools have been proposed to help stratify the risk of unfavorable outcomes over the clinical course of acute PE.

The Pulmonary Embolism Severity Index (PESI) is a tool that was developed from a retrospective study of data from a large database of records for patients treated in the United States; the study included an initial sample of 10,354 patients who were discharged from the hospital with a diagnosis of acute PE and a subsequent subsample of 5,177 patients for internal validation.[2] The objective of the PESI was to stratify the risk of death after identification of acute PE, on the basis of objective clinical parameters, in order to help guide treatment. A logistic regression model identified 11 clinical variables as independent predictors of overall 30-day mortality. A model with β coefficients attributed a different weight to each of those variables. On the basis of the total score on the PESI,[2] patients were grouped into five categories (Table 1): risk class I (very low risk); risk class II (low risk); risk class III (intermediate risk); risk class IV (high risk); and risk class V (very high risk).

The PESI has been validated in population-based samples from different countries.[3-5] In 2014, the European guidelines for the diagnosis and treatment of acute PE included this tool in their treatment guidance flowchart.[1] However, to our knowledge, there have been no studies validating the PESI for use in Brazil. The objective of the present study was to validate the PESI in a retrospective cohort of patients with a diagnosis of acute PE in Brazil.

METHODS

This was a single-center retrospective cohort study involving patients admitted to the Emergency Department of the University of São Paulo at Ribeirão Preto School

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Table 1. Parameters used in the Pulmonary Embolism Severity Index for overall 30-day mortality risk stratification after acute pulmonary embolism.

Parameter	Original version	Simplified version
Age, years	+ n of years	1 point (if > 80 years)
Male gender	+ 10 points	-
Cancer	+ 30 points	1 point
Heart failure	+ 10 points	1 point
COPD	+ 10 points	
HR ≥ 110 bpm	+ 20 points	1 point
SBP < 100 mmHg	+ 30 points	1 point
RR > 30 breaths/min	+ 20 points	-
Temperature < 36°C	+ 20 points	-
Altered mental status	+ 60 points	-
SpO_2 < 90%	+ 20 points	1 point
Risk stratification (based on the total score)		
Class I	< 65 points	0 points
Class II	65-85 points	
Class III	86-105 points	≥ 1 point
Class IV	106-125 points	
Class V	> 125 points	

SBP: systolic blood pressure.

of Medicine *Hospital das Clínicas*, located in the city of Ribeirão Preto, Brazil, with a primary diagnosis of acute PE. The hospital, which is dedicated to emergency care, is a tertiary referral center for the 26 municipalities within the XIII Regional Health Care Division of the São Paulo State Health Department and treats an average of approximately 20,000 patients per year. The study was approved by the local research ethics committee (Ruling no. 919/2016) and was conducted in accordance with the Declaration of Helsinki.

Data collection

We reviewed the medical records of all patients admitted to the emergency department between January of 2009 and December of 2015 with a primary diagnosis of acute PE, recorded on electronic discharge forms as code I26.0 (pulmonary embolism with acute *cor pulmonale*) or I26.9 (pulmonary embolism without acute *cor pulmonale*) of the International Classification of Diseases, 10th revision (ICD-10). A definitive diagnosis of acute PE was defined as the presence of a clinical profile consistent with acute PE plus at least one confirmatory criterion: filling defects on CT angiography of the pulmonary arteries; ventilation/perfusion lung scintigraphy findings of perfusion defects in ventilated areas (high probability); intraluminal filling defects on conventional pulmonary angiography; leg ultrasound findings consistent with deep vein thrombosis; or autopsy findings identifying lobar or central embolism without evidence of any other alternative diagnoses.

For those patients with a definitive diagnosis of acute PE, we calculated the original and simplified versions of the PESI. To that end, we used clinical data from medical records created at hospital admission. If any parameter used in the PESI was missing from the medical record, the index was calculated in the same way, without the inclusion of that missing item. According to the values obtained, patients were classified into one of the five risk classes of the original version and into one of the two risk classes of the simplified version, as described in the literature (Table 1). Other demographic and clinical data that are not used in the PESI were obtained through a review of medical records.

The outcome measure assessed in the present investigation was the overall 30-day mortality rate, an outcome measure that is identical to that of the original study.[2] Patients who were discharged from the hospital before completing the 30-day follow-up were contacted by telephone. The telephone contact was made by a member of the clinical research unit of our institution, who was properly trained in analyzing survival. When a death was confirmed, the date of death was requested.

Statistical analysis

Categorical variables were expressed as frequency and proportion. Continuous variables with normal distribution were expressed as mean and standard deviation, whereas the other variables were expressed as median and interquartile range. To compare overall 30-day mortality rates across the different risk classes, we calculated relative risk (RR) and the corresponding 95% CI, subsequently applying the chi-square test. To analyze survival, we constructed various Kaplan-Meier curves, which we compared using the log-rank test. To compare prognostic accuracy between the original version and the simplified version, we constructed ROC curves and examined the area under the curve (AUC) for each. Given the study design, no sample size estimation was performed. Statistical significance was defined as a two-tailed $p \leq 0.05$. We performed the statistical analysis and constructed graphs using

STATA software, version 13.1 (StataCorp LP, College Station, TX, USA).

RESULTS

During the study period, 231 patients with a primary diagnosis of acute PE were admitted to the emergency department. After a detailed review of medical records, 123 patients were found to meet the criteria for a definitive diagnosis of acute PE according to the parameters established in the present study.

For 6 of the 11 parameters used to calculate the PESI, data were available in the medical records of all 123 patients included in the study. The proportions of patients for whom medical record data were available for the other 5 parameters were as follows: 99% for altered mental status; 97% for systolic blood pressure < 100 mmHg; 93% for RR > 30 breaths/min; 89% for temperature < 36°C; and 89% for SpO_2 < 90%.

The demographic, clinical, and laboratory characteristics of these patients with a definitive diagnosis of acute PE are shown in Table 2. The mean age of the patients was 57 ± 17 years, and there was a predominance of females, who accounted for 60% of the cohort. The most common clinical finding was dyspnea (in 81%), followed by any chest pain (in 33%), leg pain (in 33%), cough (in 32%), signs of deep vein thrombosis (in 30%), and pleuritic chest pain (in 29%). The other signs and symptoms were less prevalent. The median time to the onset of the clinical presentation was 3 days (range: 1-18 days). The presence of circulatory shock and cardiopulmonary arrest was observed in 13 patients (11%) and 9 patients (7%), respectively. The most common predisposing factors were obesity (in 38%), immobilization for more than 3 days (in 31%), previous deep vein thrombosis (in 23%), and recent surgery (in 15%). The presence of active neoplasia was documented in 8 patients (7%).

CT angiography was the diagnostic imaging test most commonly used (in 80%); ventilation/perfusion lung scintigraphy and ultrasound of the lower limbs were used in smaller proportions of patients. Conventional pulmonary angiography was not used as a diagnostic instrument in any of the cases analyzed. The definitive diagnosis was confirmed by autopsy in only 5 patients, all of whom were admitted with cardiopulmonary arrest and rapidly progressed to death before any confirmatory imaging test was performed.

With regard to treatment, 32 patients (26%) received thrombolytic agents; of those, 22 were hemodynamically unstable and 10 were hemodynamically stable. The use of thrombolytic agents in this latter group remains controversial in the literature, and these cases were selected by the medical team for this type of treatment because of significant functional impairment, the need for increased supplemental oxygen, high thrombotic load, marked pulmonary hypertension, and right ventricular dysfunction. Most of the patients received systemic heparinization, with low-molecular-weight heparin (in 73%) or unfractionated heparin (in 20%).

Table 2. Demographic, clinical, and laboratory characteristics of the patients diagnosed with acute pulmonary embolism who were included in the study, at the time of hospital admission (N = 123).[a]

Characteristic	Result
Demographic	
Age, years	57 ± 18
Male gender	49 (40)
Race	
White	100 (81)
Black	23 (19)
Clinical findings	
Dyspnea	100 (81)
Any chest pain	40 (33)
Leg pain	40 (33)
Cough	39 (32)
Signs of DVT	37 (30)
Pleuritic chest pain	36 (29)
Syncope	20 (16)
Fever	17 (14)
Circulatory shock	13 (11)
Hemoptysis	11 (09)
Cardiopulmonary arrest	09 (07)
Duration of symptoms, days	03 [1-6]
RR, breaths/min	24 [19-30]
SpO_2 on room air, %	92 [87-95]
SBP, mmHg	120 [110-130]
DBP, mmHg	75 [70-90]
HR, bpm	96 [84-109]
Shock index (HR/SBP)	0.87 ± 0.27
Risk factors	
Obesity	47 (38)
Immobilization > 3 days	38 (31)
Previous DVT	28 (23)
Recent surgery < 1 month prior	18 (15)
Fracture	17 (14)
Heart failure	16 (13)
Previous stroke	15 (12)
Oral contraceptive use	13 (11)
Thrombophilia	12 (10)
COPD	10 (08)
Active neoplasia	08 (07)
Diagnostic method	
CT angiography	99 (80)
DVT ultrasound of legs	11 (09)
V/P lung scintigraphy	08 (07)
Autopsy	05 (04)
Treatment	
Low-molecular-weight heparin	90 (73)
Thrombolytic agents	32 (26)
Unfractionated heparin	24 (20)
Vena cava filter	03 (02)

SBP: systolic blood pressure; DBP: diastolic blood pressure; DVT: deep vein thrombosis; and V/P: ventilation/perfusion. [a]Values expressed as mean ± SD, n (%), or median [interquartile range].

Nine patients did not receive any type of heparinization, 5 because of rapid progression to death, due to the fact that they were admitted with cardiopulmonary arrest, and 4 because of contraindications, such as coagulopathy, thrombocytopenia, or bleeding. Of the 4 patients with contraindications, 1 underwent surgical embolectomy and 3 received an inferior vena cava filter.

There were 28 deaths, translating to an overall 30-day mortality rate of 23%. Among the patients who died, the PESI risk classes were distributed as follows: class I, in 0.80%; class II, in 1.70%; class III, in 4.90%; class IV, in 3.25%; and class V, in 12.20% ($p < 0.0001$). The cluster analysis based on the original version showed that overall 30-day mortality was higher for classes III-IV-V (20.00%) than for classes I-II (2.40%)—RR = 5.9; 95% CI: 1.88-18.51; $p = 0.0002$; with a negative predictive value of 94% and a positive predictive value of 35%. When we calculated overall 30-day mortality using the simplified PESI (0 points vs. ≥ 1 point), we found it to be 3.2% for 0 points and 19.5% for ≥ 1 point (RR = 2.38; 95% CI: 0.89-6.38; $p = 0.06$), with a negative predictive value of 88% and a positive predictive value of 35% (Table 3).

A survival analysis with Kaplan-Meier curves, using the original version, showed that risk classes I and II presented similar curves ($p = 0.59$), as did risk classes III, IV, and V ($p = 0.25$). However, a comparison of the Kaplan-Meier curves of the clusters based on the original version showed significantly higher overall 30-day mortality in risk classes III-IV-V than in risk classes I-II (RR = 7.63; 95% CI: 2.29-25.21; $p = 0.0001$; Figure 1). An analysis of the Kaplan-Meier curves for the simplified version (0 points vs. ≥ 1 point) showed that overall 30-day mortality was higher for 0 points than for ≥ 1 point (RR = 2.95; 95% CI: 1.02-8.51; $p = 0.03$).

An ROC curve comparison of prognostic accuracy for determining overall 30-day mortality revealed that the cluster analysis based on the original version had greater accuracy than did the analysis based on the simplified version, with an AUC of 0.70 (95% CI: 0.62-0.77) vs. 0.60 (95% CI: 0.51-0.67; $p = 0.05$; Figure 2).

DISCUSSION

The present investigation showed that the PESI adequately predicted the prognosis after an episode of acute PE in this sample of the population of Brazil and that the cluster analysis based on the original version is the most appropriate way to use this tool.

One notable finding of the present study is the high overall 30-day mortality rate (23%). In addition, the prevalence of circulatory shock in the initial clinical presentation was high (11%). A study conducted in the United States,[6] using real-world records of patients diagnosed with acute PE in the emergency department, reported an overall 30-day mortality rate of 5.4% and a prevalence of circulatory shock of 3.0% in a population-based sample with demographic characteristics very similar to those observed in our investigation, both in terms of age (56 ± 18 years vs. 57 ± 18 years; $p = 0.766$) and in terms of a predominance of females (53% vs. 60%; $p = 0.11$).[6] We speculate that several factors, such as delayed diagnosis of acute PE and delayed initiation of heparinization in patients in a public hospital setting in Brazil, could be responsible for these findings in our study.

To our knowledge, there is only one multicenter registry in Brazil that included 727 patients with a diagnosis of acute PE admitted to the emergency department or the ICU and that also found a high in-hospital mortality rate (19.5%),[7] which was very similar to that reported in our investigation. A separate analysis of data from that same registry also showed a high (14.1%) overall mortality rate even in the subgroup of hemodynamically stable patients.[8]

Table 3. Data on prevalence and overall 30-day mortality observed in patients with acute pulmonary embolism in the present study, by classification according to the original Pulmonary Embolism Severity Index (PESI), the clusters based on the original PESI, and the simplified PESI, and comparison with data reported in the international literature.[a]

Classification	Prevalence	Overall 30-day mortality	Variation in overall 30-day mortality (%)[b]
Original version			
Risk class I, very low	25 (20)	01 (0.80)	0.0-1.6
Risk class II, low	26 (21)	02 (1.70)	1.7-3.5
Risk class III, moderate	24 (20)	06 (4.90)	3.2-7.1
Risk class IV, high	15 (12)	04 (3.25)	4.0-11.4
Risk class V, very high	33 (27)	15 (12.20)	10.0-24.5
Total	123 (100)	28 (23.00)	
Clusters based on the original version			
Risk classes I-II	51 (41)	03 (02.40)	
Risk classes III-IV-V	72 (59)	25 (20.00)	
Simplified version			**Variation in overall 30-day mortality, % (95% CI)**
0 points	35 (28)	04 (03.20)	1.0 (0.0-2.1)
≥ 1 point	88 (72)	24 (19.50)	10.9 (8.5-13.2)

[a]Values expressed as n (%), except where otherwise indicated. [b]According to references 1-5.

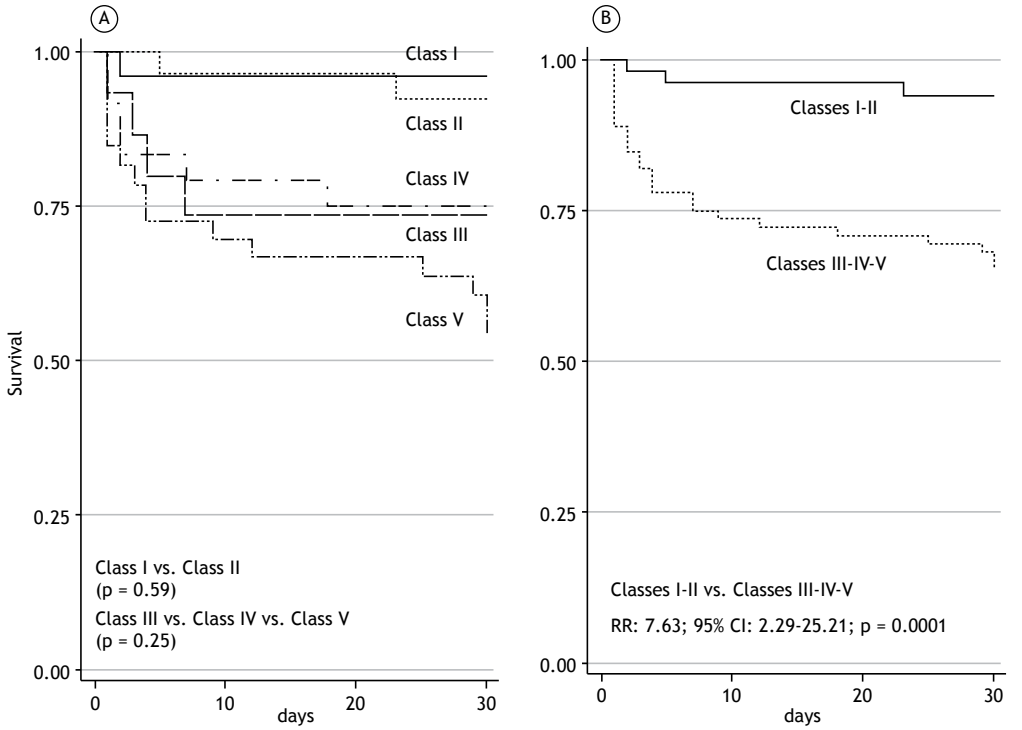

Figure 1. Kaplan-Meier curves showing 30-day survival in patients diagnosed with pulmonary embolism, by each of the five Pulmonary Embolism Severity Index risk classes (in A) and by cluster (risk classes I-II vs. risk classes III-IV-V; in B). RR: relative risk.

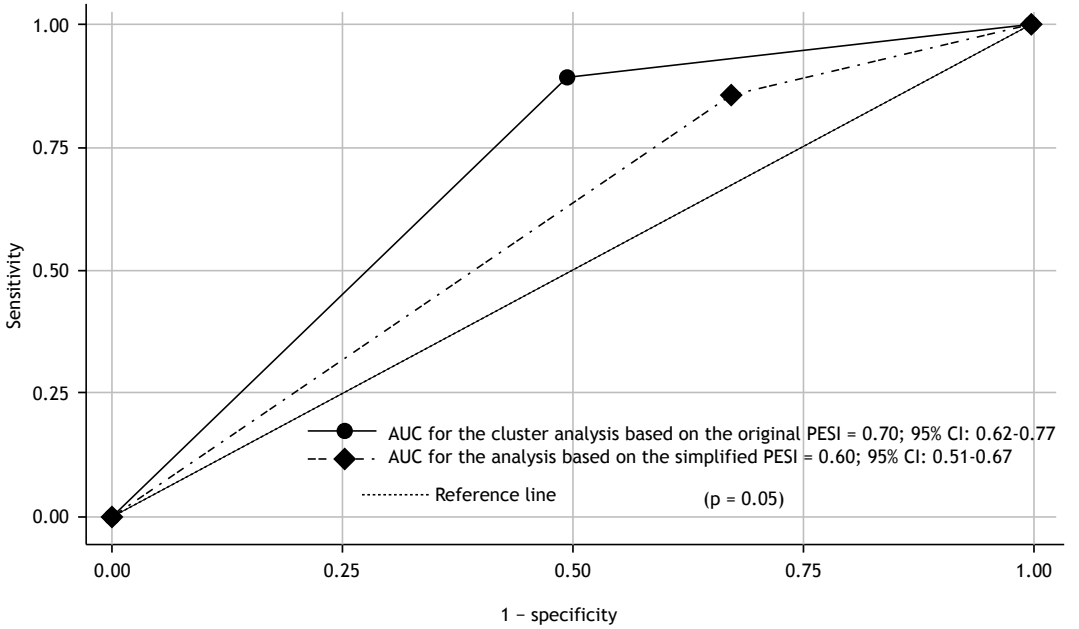

Figure 2. ROC curve comparison of prognostic accuracy for predicting overall 30-day mortality after acute pulmonary embolism between the cluster analysis based on the original Pulmonary Embolism Severity Index (PESI) and the analysis based on the simplified PESI. AUC: area under the (ROC) curve.

A large international registry[9] showed an overall 30-day mortality rate of 3.3% (95% CI: 2.9-3.8%), which is also very similar to that reported by Pollack et al.[6] In contrast, a study by Goldhaber et al.[10] showed a 14-day mortality rate of 11.2% (95% CI: 10.0-12.5%), which is higher than that found in other international registries,[8,9] probably because it included an older population. It is important to emphasize that the data of the present investigation are mainly related to a primary diagnosis of acute PE as the cause of hospital admission and that these data are not representative of acute nosocomial PE.

When we analyzed overall 30-day mortality by PESI risk class, we found that the rates were similar to those reported in the international literature,[1-5] especially those reported in the study that originally described the PESI.[2] The exception was risk class IV, for which the overall 30-day mortality rate was slightly lower in our study than in the first validation study (3.25% vs. 4.0-11.0%).[2] It is worth noting that risk class IV had the lowest prevalence in our study (12.20%), as it did in the original study,[2] where its prevalence ranged from 11.30% to 16.40%. Another important factor is that, in the study that described the PESI,[2] the overall 30-day mortality rate for risk class IV was higher in the initial sample and the internal validation sample (10.40% and 11.40%, respectively), whereas it was proportionally lower (4.0%) in the external PESI validation sample.[2] This last value is very close to that observed in our study. In addition, as has been shown in the scientific literature,[11] our investigation showed that the cluster analysis based on the original version, in which risk classes III-IV-V are analyzed as a group rather than individually, seems to be the most appropriate.[11]

One of the major advantages related to the use of the PESI is the selection of a group of patients at low risk for complications, characterized as risk class I-II, who may be discharged from the hospital early and undergo home treatment, thus reducing hospital costs.[12-14] Our investigation also showed that the prognosis was good in the patients in this group (risk class I-II), with a reduced overall 30-day mortality rate. Nevertheless, it is worth noting that early hospital discharge resulting from the use of new anticoagulants does not typically occur at the locale under study, especially during the period evaluated.

Like other prognostic markers in the assessment of acute PE, the cluster analysis based on the original PESI has a high negative predictive value (94%) but a low positive predictive value (35%). Therefore, the PESI is more useful in selecting those patients with a good prognosis, and the presence of patients in risk classes III-IV-V does not necessarily imply the occurrence of adverse events and the need for more aggressive therapy.[15] The 2014 European guidelines for the management of acute PE[1] recommend the use of a new risk stratification method based on biomarkers such as troponin and NT-proBNP, as well as on imaging tests for assessing the right ventricle, in patients in risk classes III-IV-V.

Our results are also in line with those in the literature[11]: the cluster analysis based on the original version (risk classes I-II vs. risk classes III-IV-V) seems to be the most appropriate way to use this instrument, as shown by the good evidence obtained from the Kaplan-Meier curves (Figure 1). This form of analysis divides patients into two groups with very different prognosis (overall 30-day mortality of 2.40% vs. overall 30-day mortality of 20.00%). A recent systematic review and meta-analysis[11] that evaluated prognostic models in acute PE showed overall 30-day mortality rates of 2.30% and 11.40%, respectively, in the low-risk group (PESI risk classes I-II) and high-risk group (PESI risk classes III-IV-V). The mortality observed in the low-risk group in our investigation (2.40%) is similar to the 2.30% observed in that study.[11]

Given that numerous variables are involved in the original PESI, an attempt was made to develop a simplified version including only 6 variables that have similar weights in the calculation of the index. That version is known as simplified PESI. One early study showed no difference in prognostic accuracy between the original version and the simplified version, with identical AUC of 0.75 (95% CI: 0.69-0.80; p = 0.95).[16] However, a subsequent investigation showed that the prognostic accuracy of the original version was higher than that of the simplified version, with an AUC of 0.78 (95% CI: 0.77-0.79) vs. 0.72 (95% CI: 0.71-0.74; p < 0.001),[17] similarly to our investigation, in which the original version was also found to be slightly superior to the simplified version, with an AUC of 0.70 (95% CI: 0.62-0.77) vs. 0.60 (95% CI: 0.51-0.67; p = 0.05). It is important to emphasize that, in our investigation, the prognostic accuracies of both versions were slightly lower than those reported in the international literature.[17]

Some limitations of the present investigation are worthy of note. First, because data were collected retrospectively from medical records, not all of the data needed to calculate the PESI were available for some patients. That may have resulted in the final value of the PESI being underestimated in a small portion of the sample. However, the proportion of individuals with incomplete medical records was small and therefore had little influence on the final results of the present investigation. In addition, it was possible to assess the outcome measure (overall 30-day mortality) in all of the patients included in the present analysis. It is worth emphasizing that the outcome assessed was overall 30-day mortality, which does not necessarily reflect mortality associated with acute PE; however, most studies validating the PESI have also used this same outcome.[2,4] Second, this was a single-center study conducted at a tertiary referral hospital dedicated to emergency care, which may have led to the selection of patients with greater disease severity, potentially creating a selection bias, similarly to that seen in another study on acute PE conducted in Brazil.[7] Third, our retrospective review of patient medical records was based on the ICD-10 codes recorded on electronic discharge forms. That may have caused the non-inclusion of some patients. Fourth, because the PESI is based on quantitative clinical parameters that are quite objective, we considered that other steps of the validation process, such as back-translation and cross-cultural validation, were unnecessary. A positive point of our investigation was that confirmation of the diagnosis by complementary imaging was mandatory, unlike many of the studies validating the PESI that have been published in the literature,[2,4] all of which

used only hospital admission databases coded for acute PE and did not require confirmation of the diagnosis by imaging.

The PESI adequately predicted the prognosis after acute PE in this sample of the population of Brazil. The cluster analysis based on the original version is the most appropriate way to use this tool in this setting. Although the overall 30-day mortality rate after acute PE observed in our sample is high when compared with that reported in international studies,[6,9,10] it is in agreement with data from a study on this topic conducted in Brazil.[7] It is necessary that prospective multicenter studies be conducted in Brazil, in order to further assess mortality associated with acute PE in our population.

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Prevalence of vitamin D deficiency and its relationship with factors associated with recurrent wheezing

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ABSTRACT

Objective: To determine the prevalence of vitamin D deficiency/insufficiency in children 0-18 years of age with recurrent wheezing and/or asthma residing in the microregion of Viçosa, Minas Gerais, Brazil, and treated at a referral center, and to determine its association with major risk factors for wheezing. **Methods:** A cross-sectional study was performed using a semi-structured questionnaire, which was administered by trained interviewers to the legal guardians of the study participants. Data were obtained regarding general characteristics of recurrent wheezing; general sociodemographic, environmental, and biologic factors; and atopy-related factors. The magnitude of the statistical association was assessed by calculating ORs and their corresponding 95% CIs by using multiple logistic regression. **Results:** We included 124 children in the study. The prevalence of vitamin D deficiency/insufficiency in the sample was 57.3%. Vitamin D deficiency/insufficiency was found to be associated with wheezing in the first year of life, personal history of atopic dermatitis, environmental pollution, and vitamin D supplementation until 2 years of age. **Conclusions:** The prevalence of vitamin D deficiency/insufficiency was high in our sample. Vitamin D concentrations were directly associated with vitamin D supplementation until 2 years of age and were inversely associated with wheezing events in the first year of life, personal history of atopic dermatitis, and environmental pollution.

Keywords: Vitamin D; Asthma; Respiratory sounds; Minors.

INTRODUCTION

Studies in animal models and humans have demonstrated an association of low vitamin D concentrations with atopy and respiratory tract conditions. The mechanism that explains this association is still unclear. It has been suggested that this mechanism is due to the effects of vitamin D status on the regulation of the immune system.[1]

The vitamin D receptor is expressed in various cells of the immune system, such as macrophages, monocytes, dendritic cells, and natural killer cells, as well as in B and T lymphocytes. Binding of the active form of vitamin D to its receptor leads to an increase in immunomodulatory activity that maintains the balance between the cellular immune response (Th1) and the humoral response (Th2), in addition to stimulating regulatory T cells.[2]

The prevalence of atopic diseases, especially chronic respiratory diseases, such as asthma and recurrent wheezing in childhood, is increasing both in Brazil and worldwide. These diseases represent an important cause of morbidity and mortality in the pediatric age group. They are considered a public health problem because they affect the quality of life of these patients, given frequent use of the health care system, causing great economic impact.[3,4]

Various risk factors are associated with recurrent wheezing and asthma: small airway caliber; decreased lung function at birth; viral respiratory infections; environmental pollution; pets; early daycare attendance; passive smoking; parental history of asthma or atopy; obesity; and socioeconomic factors. In this context, vitamin D plays a prominent role as a risk factor for increased prevalence of allergic diseases.[5] Therefore, the objective of the present study was to analyze the prevalence of vitamin D deficiency/insufficiency and its relationship with factors associated with recurrent wheezing and asthma in a population of children with this symptom/disease.

METHODS

Study design

This was a cross-sectional study of 124 pediatric patients followed in the Pulmonology Outpatient Clinic of the State Referral Center for Specialized Care, in the

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municipality of Viçosa, Minas Gerais, Brazil, conducted between November 2016 and September 2107. The present study was approved by the Human Research Ethics Committee of the Federal University of Viçosa (Ruling no. 1,713,903).

The State Center for Specialized Care is the only referral facility for pediatric pulmonology in the microregion of Viçosa, serving approximately 20 municipalities. Treatment is provided by an interdisciplinary team, including professionals in the areas of physical therapy, nutrition, psychology, nursing, social work, and medicine, in partnership with the Federal University of Viçosa.

The following inclusion criteria were used to select the present study sample: having recurrent wheezing and/or asthma, being followed in the aforementioned outpatient clinic, and legal guardians providing written informed consent; residing in Viçosa or in the microregion of Viçosa during the data collection period; and being 0 to 18 years of age. The exclusion criteria were as follows: having refused to participate in the study; and having associated diseases (e.g., heart diseases, cystic fibrosis, gastroesophageal reflux disease, pneumonia, pulmonary tuberculosis, bronchopulmonary dysplasia, cerebral palsy, congenital lung malformations, immunodeficiencies, or post-infectious bronchiolitis obliterans). A semi-structured questionnaire, based on the standardized International Study of Asthma and Allergies in Childhood questionnaire and including sociodemographic variables (gender, race, age group, level of maternal education, level of parental education, family income, and daycare or school attendance), was used.[6]

During the study period, two peripheral blood samples were collected from each patient (into a tube without anticoagulant for analysis of vitamin D and into an EDTA-containing tube for a complete blood count). Serum 25-hydroxyvitamin D concentrations were measured with a competitive chemiluminescence immunoassay (DiaSorin, Stillwater, MN, USA). The outcome variable, serum vitamin D concentration, was expressed in ng/mL, with deficiency, insufficiency, and sufficiency being defined as values below 20, values between 21 and 29, and values above 30, respectively.[7]

Statistical analysis

In the statistical analysis of variables, absolute and relative frequencies were calculated. In addition, in the analysis of distribution normality, continuous numerical variables were described by their means and standard deviations. Explanatory variables were tested for independence from the outcome variable using the chi-square test, and those showing significant differences at a level less than or equal to 20% ($p \leq 0.20$) were considered for multivariate analysis. Since the vitamin D variable did not meet the linear regression assumptions, we chose to use logistic regression. To that end, the vitamin D variable was categorized as sufficient or insufficient/deficient. The magnitude of the statistical association between vitamin D concentrations and the other variables was assessed by calculating odds ratios and their corresponding 95% confidence intervals by using multiple logistic regression. We used the Stata statistical software package, version 10 (Stata Corp., College Station, TX, USA).

Given the objectives of the study, the final regression model was selected on the basis of inclusion of all explanatory variables that showed significance ($p < 0.20$) in bivariate analysis. Variables were then selected according to their statistical significance. The equation was evaluated at each step, and the procedure was repeated until all variables remaining in the final equation had a p value ≤ 0.05, with these variables being responsible for explaining the variance observed in the outcome variable.

RESULTS

One hundred and twenty-four patients registered at the pediatric pulmonology clinic of the State Center for Specialized Care during the study period participated in the study. We found that most were male and were declared non-White (biracial or Black) and that the mean age was 5.8 ± 4.6 years. Most participants attended daycare or school, and 77 (62.1%) were born by cesarean section. Of the total sample, 97 participants (78.2%) had a monthly family income of ≤ 2 times the national minimum wage. Other sociodemographic data are shown in Table 1.

With regard to clinical characteristics, slightly more than half of the children had experienced wheezing in the first year of life as well as in the last four weeks. In the 12 months preceding the interview, 67 (54.0%) visited the emergency room and 37 (29.8%) required hospitalization due to wheezing exacerbation (Table 2).

The prevalence of vitamin D deficiency/insufficiency among the participants was 57.3%. There were no significant race-related differences in vitamin D concentrations. However, we found significantly higher vitamin D concentrations in children in the 0-36-month age group than in those in the 37-72-month age group (Figure 1).

At the time of the interview, 57.1% of the children aged up to 24 months (n = 21) were receiving vitamin D supplementation as recommended by the Brazilian Society of Pediatrics.[8] However, we found that 50.8% of the study sample did not receive vitamin D supplementation in the first 2 years of life.

In bivariate analysis, the following variables had a p value < 0.20 for vitamin D status: onset of wheezing before age 1 year; physician-diagnosed asthma; personal history of atopic dermatitis; family history of rhinitis; daycare or school attendance; pets in the household before birth; environmental pollution; oral corticosteroid use during exacerbations;

Table 1. Sociodemographic characteristics of the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

Characteristic	n	%
Age group		
< 3 years	31	25.0
3-6 years	47	37.9
> 6 years	46	37.1
Gender		
Female	48	38.7
Male	76	61.3
Race		
White	25	20.2
Non-White	99	79.8
Level of maternal education		
≤ 8 years of schooling	41	33.1
9-11 years of schooling	33	26.6
≥ 12 years of schooling	50	40.3
Level of paternal education		
≤ 8 years of schooling	72	58.1
9-11 years of schooling	21	16.9
≥ 12 years of schooling	30	24.2
No answer	1	0.8
Family income, number of times the national minimum wage		
≤ 1	54	43.5
[1-2]	43	34.7
> 2	27	21.8
Attends daycare or school		
No	28	22.6
Yes	96	77.4

vitamin D supplementation in the first 2 years of life; breastfeeding; and eosinophilia. After multiple logistic regression analysis, the variables that remained associated with vitamin D status were onset of wheezing before age 1 year, personal history of atopic dermatitis, environmental pollution, and vitamin D supplementation in the first 2 years of life (Figure 2).

DISCUSSION

In the present study, the first relevant finding was the high prevalence of vitamin D deficiency/insufficiency (57.3%) in patients with recurrent wheezing and/or asthma registered at our facility. In a systematic review, vitamin D deficiency/insufficiency was observed in 55.2% of the children with asthma, and mean 25-hydroxyvitamin D levels were significantly lower in children with asthma than in those without asthma.[9]

Studies in the literature have increasingly suggested the existence of a relationship between serum vitamin D concentrations and respiratory symptoms, presumably because of the immunomodulatory effects of vitamin D.[9] The increased prevalence of vitamin D deficiency/insufficiency in the pediatric population is currently considered a public health problem. Changes in the environmental factors associated with the new urban lifestyles, such as remaining longer indoors, little sun

Table 2. Clinical characteristics of the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

Characteristic	n	%
Onset of wheezing before age 12 months		
NO	55	44.4
YES	69	55.6
Wheezing in the last 4 weeks		
NO	54	43.5
YES	70	56.5
Emergency room visits in the last 12 months		
NO	57	46.0
YES	67	54.0
Need for hospitalization		
NO	87	70.2
YES	37	29.8
Diagnosis of pneumonia		
NO	84	67.7
YES	40	32.3
Hospitalization for pneumonia		
NO	92	74.2
YES	32	25.8
Received inhaled corticosteroid treatment		
NO	34	27.4
YES	90	72.6
Currently receiving inhaled corticosteroid treatment		
NO	65	52.4
YES	59	47.6
Received leukotriene receptor antagonist treatment		
NO	113	91.1
YES	8	6.5
I DON'T KNOW	3	0.3
Oral corticosteroid use		
NO	12	9.8
YES	111	90.1
I DON'T KNOW	1	0.1

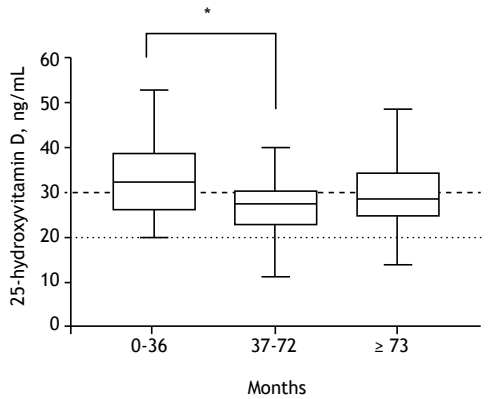

Figure 1. Stratification of serum vitamin D concentrations, as quantified by chemiluminescence, by age group. (...) deficiency threshold; and (---) insufficiency threshold. *p < 0.04.

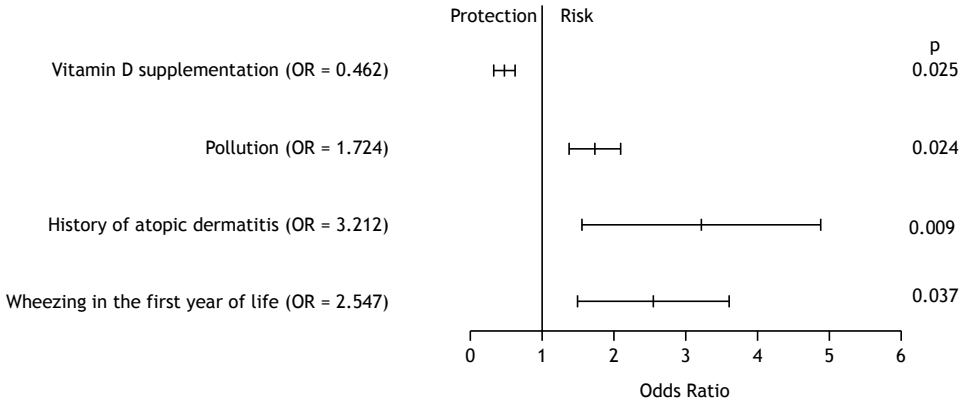

Figure 2. Independent protective and risk factors for vitamin D deficiency/insufficiency in the study population (N = 124), Viçosa, Minas Gerais, Brazil, 2016-2017.

exposure, and a sedentary lifestyle, may be associated with the increased prevalence of this condition.[9]

In the present study, environmental pollution showed an inverse association with serum vitamin D concentrations. It is known that regions that are more polluted, especially those with high ozone levels, which is common in large cities, tend to absorb ultraviolet type B radiation, causing a reduction in the efficacy of sun exposure for producing vitamin D in the skin.[10]

A study comparing serum vitamin D concentrations between infants residing in a region with high levels of air pollution in New Delhi, India, and children in a less polluted area found that those residing in highly polluted areas were at an increased risk of developing vitamin D deficiency and rickets.[10]

In our study, we also observed that low serum vitamin D concentrations were associated with onset of wheezing before age 1 year and personal history of atopic dermatitis. Viral infections, especially those caused by respiratory syncytial virus and rhinovirus, are known to be the major causes of wheezing in the first years of life.[11] Epidemiological data have shown a relationship between vitamin D deficiency and increased susceptibility to acute viral respiratory tract infections.[12] A case-control study investigated severity of vitamin D deficiency and its association with recurrent wheezing in children under 3 years of age.[13] The authors reported that, for every 10 ng/mL decrease in vitamin D concentration, there was a 7.25% increase in the probability of wheezing. The results support the hypothesis that low serum vitamin D concentrations are associated with respiratory morbidity in infants with recurrent wheezing.[13]

Atopic dermatitis is a chronic, relapsing disease of unknown etiology. Its major characteristic is deficiency in skin barrier function due to abnormal lipid metabolism, resulting in drier skin. Another important factor in atopic dermatitis is immune deviation to a Th2 response, leading to greater production of IL-4, IL-13, and IgE. These interleukins can suppress antimicrobial peptide production, causing a change in the skin microbiota and, consequently, greater susceptibility to skin infections, especially with *Staphylococcus aureus*.[14]

Laboratory studies have suggested that vitamin D stimulates expression of antibacterial peptides, such as cathelicidin and filaggrin, strengthening innate immunity and increasing microbicidal capacity against fungi, viruses, and bacteria, especially *S. aureus*, which contributes to persistent skin inflammation. A study of patients with atopic dermatitis found an inverse relationship between serum vitamin D concentrations and the disease. In a meta-analysis, vitamin D was found to play an important role in the improvement of the symptoms of atopic dermatitis.[15,16]

There is growing evidence that maternal vitamin D intake during pregnancy has a protective effect against wheezing and atopic dermatitis. In a cohort study of 239 children that aimed to evaluate associations of 25-hydroxyvitamin D concentrations in umbilical cord blood with asthma, wheezing, allergic rhinitis, and atopic dermatitis from birth to age 5 years, an inverse association was found between serum 25-hydroxyvitamin D concentrations and risk of transient early wheezing and atopic dermatitis in the first years of life, suggesting that adequate vitamin D intake and optimal serum vitamin D concentrations reduce the risk of wheezing, especially virus-induced wheezing.[15,16]

It was interesting to note in our study that there was a high prevalence of patients who did not receive vitamin D supplementation until 2 years of age, as recommended by the Brazilian Society of Pediatrics.[7,17] Vitamin D supplementation for patients with recurrent wheezing and/or asthma remains a controversial issue; however, universal vitamin D supplementation in the first 2 years of life for bone health is well established. Since vitamin D supplementation early in life decreases the risk of vitamin D deficiency, raising awareness of health care professionals and family members about the importance of this public policy strategy is relevant.[18]

Although in the present study vitamin D concentrations were not associated with exacerbations, as assessed on the basis of hospitalizations, emergency room visits, and oral corticosteroid use, many studies have indicated such an association.[19,20]

Some limitations to the present study should be considered. Because this was a cross-sectional study, it was not possible to establish causal relationships but rather only to report associations. In studies using questionnaires, there is also a recall bias. In an attempt to minimize this bias, we used secondary data collected from the patient medical records at our facility; the medical records are semi-structured, allowing a higher reliability in obtaining data.

One strength of the present study is that the sample size calculation enables the inference of data; in addition, the findings of the present study may motivate further studies, especially in Brazil, to elucidate the true role of vitamin D in the immune system and its relationship with atopic diseases, given that vitamin D deficiency/insufficiency is an environmental factor that can be modified by greater sun exposure and/or vitamin D supplementation.[9]

Various studies have demonstrated the high prevalence of vitamin D deficiency/insufficiency and the importance of vitamin D not only for bone health but also for other immune-mediated diseases, although the pathogenic mechanisms involved have not yet been elucidated.[21] The present study demonstrates the prevalence of vitamin D deficiency/insufficiency in pediatric patients with recurrent wheezing and/or asthma treated at a center for specialized care in the municipality of Viçosa, Minas Gerais, Brazil. Vitamin D concentrations were inversely associated with wheezing events in the first year of life, personal history of atopic dermatitis, and environmental pollution. Vitamin D supplementation proved to be a protective factor in the study population. Clinical trials are still needed to clarify the role of serum vitamin D concentrations in childhood wheezing, in asthma, and in other atopic diseases, as well as to determine optimal vitamin D levels to prevent these diseases.

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Evaluation of bone disease in patients with cystic fibrosis and end-stage lung disease

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ABSTRACT

Objective: Bone disease is a common comorbidity in patients with cystic fibrosis (CF). We sought to determine risk factors and identify potential biochemical markers for CF-related bone disease (CFBD) in a unique cohort of CF patients with end-stage lung disease undergoing lung transplantation (LTx) evaluation. **Methods:** All of the CF patients who were evaluated for LTx at our center between November of 1992 and December of 2010 were included in the study. Clinical data and biochemical markers of bone turnover, as well as bone mineral density (BMD) at the lumbar spine and femoral neck, were evaluated. Spearman's rho and multivariate logistic regression analysis were used. **Results:** A total of 102 adult CF patients were evaluated. The mean age was 28.1 years (95% CI: 26.7-29.5), and the mean body mass index was 17.5 kg/m^2 (95% CI: 17.2-18.2). Mean T-scores were –2.3 and –1.9 at the lumbar spine and femoral neck, respectively, being lower in males than in females (–2.7 vs. –2.0 at the lumbar spine and –2.2 vs. –1.7 at the femoral neck). Overall, 52% had a T-score of < –2.5 at either skeletal site. The homozygous Phe508del genotype was found in 57% of patients without osteoporosis and in 60% of those with low BMD. Mean T-scores were not particularly low in patients with severe *CFTR* mutations. Although the BMI correlated with T-scores at the femoral neck and lumbar spine, serum 25-hydroxyvitamin D and parathyroid hormone levels did not. **Conclusions:** CFBD is common in CF patients with end-stage lung disease, particularly in males and patients with a low BMI. It appears that CF mutation status does not correlate with CFBD. In addition, it appears that low BMD does not correlate with other risk factors or biochemical parameters. The prevalence of CFBD appears to have recently decreased, most likely reflecting increased efforts at earlier diagnosis and treatment.

Keywords: Lung transplantation; Cystic fibrosis; Bone density; Osteoporosis.

INTRODUCTION

Cystic fibrosis (CF) is a common life-shortening autosomal recessive genetic disorder that affects multiple organs and is caused by mutations in the *CFTR* gene, which encodes primarily for a chloride ion channel.[1] CF-related comorbidities reduce health-related quality of life and pose an ongoing challenge for patients and treating physicians. The cause of CF-related bone disease (CFBD) is likely multifactorial; CFBD is due to both suboptimal peak bone mass acquisition and increased bone loss during adulthood, affecting up to 20% of adolescent patients and 55-65% of patients 45 years of age or older.[2] Known risk factors for the development of CFBD are male sex, low body mass index (BMI), malnutrition, advanced lung disease, and systemic corticosteroid therapy. In fact, several factors contribute to the etiology of CFBD: chronic inflammation/infection, exocrine pancreatic insufficiency/malnutrition, low levels of anabolic hormones (insulin and IGF-I), low levels of sex hormones (estradiol and testosterone), and lack of physical activity.[3-10] In addition, CFTR protein dysfunction has recently been shown to affect bone-forming osteoblasts directly by reducing the production of osteoprotegerin and COX-2 metabolite prostaglandin E2, both of which are mediators of osteogenesis.[11]

The objective of the present study was to assess the frequency of CFBD in a unique cohort of adult CF patients with end-stage lung disease evaluated for lung transplantation (LTx) at our center over nearly two decades, in order to gain a deeper understanding of contributing factors to CFBD, identify potential biochemical markers for CFBD, and assess changes in disease severity and therapies over time.

METHODS

All adult CF patients (18 years of age or older) evaluated for LTx at the University Hospital of Zurich between November of 1992 and December of 2010 were included in the study. Referral and selection of LTx candidates at our center were done in accordance with published International Society for Heart and Lung Transplantation guidelines.[12] Data on *CFTR* mutation status and patient clinical status (including parameters such as age, sex, height, weight, BMI, percent predicted FEV_1 [FEV_1%], six-minute walk distance [6MWD], infectious exacerbations

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in the previous year, and CF-related diabetes mellitus [CFRD]) were collected and tabulated. The 5-year survival rate was estimated in accordance with Liou et al.[13] In addition, patient medical records were reviewed for inhaled corticosteroid therapy, systemic corticosteroid therapy, vitamin D supplementation (at least 800 U per day), and bisphosphonate therapy. The following serum levels were measured: C-reactive protein, creatinine, albumin, fasting glucose, hemoglobin A1c, calcium (values being subsequently corrected for albumin by the following formula: measured calcium − 0.025 × albumin + 1), phosphate, bone alkaline phosphatase, 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH), osteocalcin, testosterone (in males), and estradiol (in females). In a morning spot urine sample, calcium-to-creatinine and deoxypyridinoline-to-creatinine ratios were determined. Creatinine was also measured in a 24-h urine collection in order to estimate skeletal muscle mass and glomerular filtration rate (GFR). The Cockcroft and Gault equation was used in order to calculate GFR, as proposed by Soulsby et al.[14] The relative time to first evaluation for LTx was calculated and used for multivariate regression analysis. In addition, bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) and quantitative digital radiography (Hologic® DXA System; Hologic, Inc., Marlborough, MA, USA) at the femoral neck and lumbar spine, respectively, T-scores being calculated for both sites. Osteoporosis was defined in accordance with the World Health Organization BMD criteria as a T-score of ≤ −2.5, whereas osteopenia was defined as a T-score between −1.0 and −2.5.[15]

Clinical and biochemical data are reported as means and 95% confidence intervals. The following groups of patients were evaluated: 1) females and males; 2) patients with osteoporosis (i.e., those with a T-score of ≤ −2.5 at either skeletal site) and patients without osteoporosis; and 3) patients evaluated earlier in the study period and patients evaluated later in the study period. For group comparisons, the Mann-Whitney test and the Kruskal-Wallis test were used, Fisher's exact test or the chi-square test being used for categorical variables. Continuous variables were correlated by using Spearman's rho. Univariate and multivariate logistic regression models were used in order to analyze osteoporosis (overall osteoporosis, lumbar spine osteoporosis, and femoral neck osteoporosis) and sex, as well as the relative time to evaluation for LTx and clinical parameters (BMI, FEV_1%, 6MWD, CFRD, 25(OH)D levels, phosphate levels, calcium levels, and protein levels). All statistical analyses were performed with the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA). For all analyses, values of $p < 0.05$ were considered significant. The Research Ethics Committee of the Canton of Zurich approved this retrospective study (Protocol no. EK-1593).

RESULTS

A total of 102 adult CF lung transplant candidates were included in the present study. The clinical characteristics of the study patients are shown in Table 1.

BMD values as measured by DXA were available for all patients. Of those, 8 (8%) showed normal bone mass, 41 (40%) had osteopenia, and 53 (52%) had osteoporosis at either skeletal site. Mean T-scores at the femoral neck and lumbar spine were −1.9 (95% CI: 1.73 to −2.10) and −2.3 (95% CI: −2.09 to −2.55), respectively, being lower in males than in females ($p = 0.007$ and $p = 0.004$, respectively; Figure 1).

There were no differences in clinical parameters (or medication use) between males and females, the exception being height and weight (Table 1). The mean BMI was lower in patients with osteoporosis than in those without (17.4 kg/m² vs. 18.1 kg/m²; $p = 0.007$; Table 2). No differences were found between the subgroups of patients with and without osteoporosis regarding FEV_1%, 6MWD, frequency of CF exacerbations in the previous year, use of medications, presence of exocrine pancreatic insufficiency, or CFRD (Table 2).

Table 3 shows biochemical parameters in all CF patients included in the study, by osteoporosis status (i.e., with or without osteoporosis). Although there were no significant differences between the two groups of patients, those with low T-scores (defining osteoporosis in the elderly) were more likely to have an increased calcium-to-creatinine ratio in a fasting spot urine sample ($p = 0.04$). In particular, there was no difference in serum levels of calcium, phosphate, 25(OH)D, or PTH. Borderline high (albumin-corrected) calcium levels were found in 8 patients, and PTH levels > 65 ng/L (indicating secondary hyperparathyroidism in patients with low-normal serum calcium levels) were found in 11 (Table 3). Correlations of PTH levels with 25(OH)D and calcium levels are shown in Figure 2. Although PTH levels correlated significantly with (albumin-corrected) calcium levels (Spearman's rho: −0.40; $p < 0.001$), they did not correlate with 25(OH)D levels, age, creatinine levels, GFR, albumin levels, urinary calcium-to-creatinine ratio, urinary deoxypyridinoline-to-creatinine ratio, or 24-h urinary creatinine levels. Serum levels of PTH were not increased in a substantial number of patients with decreased serum levels of 25(OH)D. In addition, serum PTH levels were not associated with increased bone resorption markers or low BMD.

As can be seen in Table 2, 50 patients (49%) were receiving vitamin D supplementation (4,000 IU plus multivitamin supplementation including vitamins A, D, E, and K), and 11 patients (11%) were receiving bisphosphonate therapy; 48 (47%) used inhaled corticosteroids on a regular basis, and 33 (32%) were on long-term systemic corticosteroid therapy. Patients using systemic corticosteroids were more likely to have low BMD ($p = 0.023$). A low BMI was found to correlate with low BMD ($p = 0.004$). Of the 102 patients included in the study, 97 (95%) had exocrine pancreatic insufficiency and were receiving pancreatic enzyme supplementation (the dose of which varied depending on their diet).

CF mutation status was known in 84 patients. Of those, 51 (61%) had a severe mutation (Table 2).

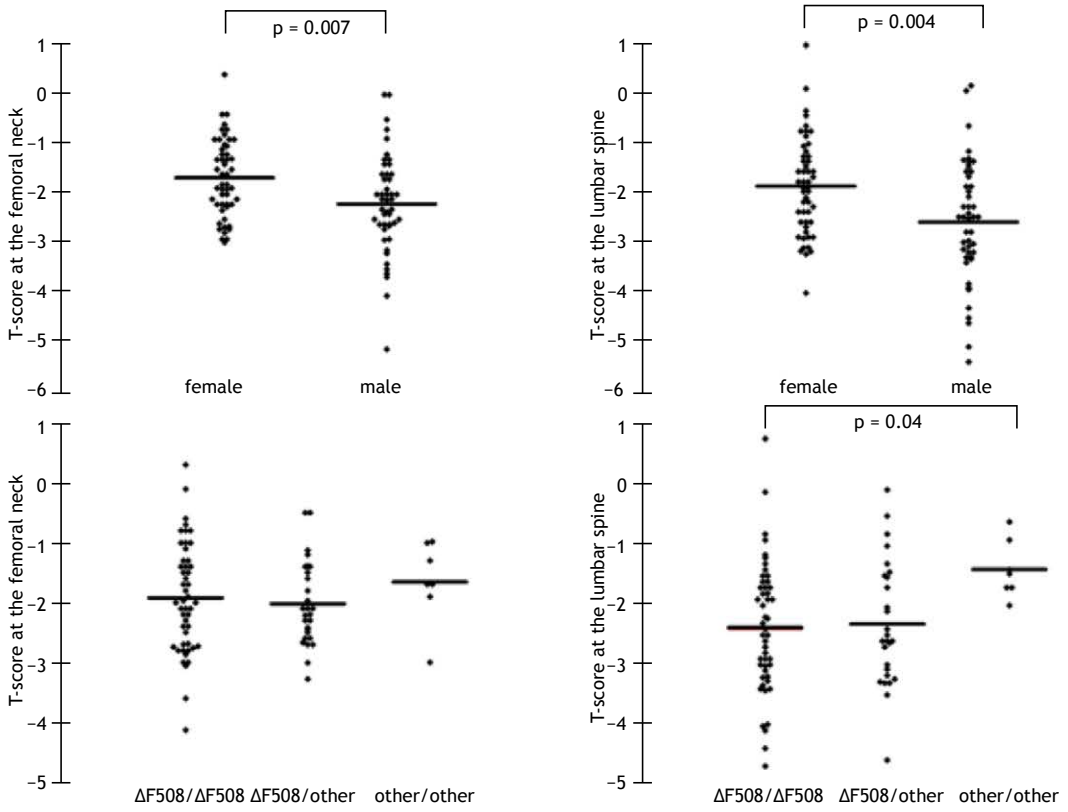

Figure 1. T-scores at the femoral neck and lumbar spine, by gender and *CFTR* gene mutation.

Table 1. Clinical characteristics of the cystic fibrosis patients included in the study.[a]

Characteristic	Total sample N = 102 (100%)	Female CF patients n = 53 (52%)	Male CF patients n = 49 (48%)	p
Age, years	28.1 (26.7-29.5)	27.5 (25.7-29.3)	28.8 (26.6-31.0)	
Height, cm	166 (164-167)	161 (160-164)	170 (168-172)	< 0.0001
Weight, kg	48 (47-50)	47 (45-49)	50 (48-53)	0.01
BMI, kg/m^2	17.5 (17.2-18.2)	18.0 (17.2-18.9)	17.4 (16.8-18.0)	
FEV_1, % predicted	25 (24-27)	27 (24-29)	24 (22-26)	
Relative time to first evaluation, years	9.9 (8.9-10.9)	10.4 (9.0-11.8)	9.3 (8.0-10.7)	
Estimated 5-year survival, %	30 (28-33)	31 (27-35)	30 (28-33)	
Osteoporosis, no/yes, n(%)	49/53 (48/52)	30/23 (57/43)	19/30 (39/61)	
T-score at the lumbar spine	−2.3 (−2.1 to −2.6)	−1.99 (−1.72 to −2.26)	−2.70 (−2.34 to −3.05)	0.004
BMD at the lumbar spine				
Normal (T-scores > −1), n (%)	11 (11)	11 (21)	8 (16)	
Osteopenia (T-scores ranging from −1 to −2.4), n (%)	41 (42)	30 (59)	25 (49)	
Osteoporosis (T-scores of ≤ −2.5), n (%)	45 (47)	10 (20)	18 (35)	
T-score at the femoral neck	−1.9 (−1.7 to −2.1)	−1.67 (−1.45 to −1.89)	−2.19 (−1.9 to −2.48)	0.007
BMD at the femoral neck				
Normal (T-scores > −1), n (%)	16 (16)	8 (16)	3 (7)	
Osteopenia (T-scores ranging from −1 to −2.4), n (%)	54 (55)	25 (49)	16 (35)	
Osteoporosis (T-scores of ≤ −2.5), n (%)	28 (29)	18 (35)	27 (59)	

CF: cystic fibrosis; BMI: body mass index; and BMD: bone mineral density. [a]Values expressed as mean (95% CI), except where otherwise indicated.

Table 2. Clinical characteristics of the cystic fibrosis included in the study, by osteoporosis status (i.e., with or without osteoporosis) and era of evaluation (i.e., earlier or later in the study period).[a]

Characteristic	Osteoporosis		Era of evaluation		p
	Without n = 49 (48%)	With n = 53 (52%)	First 51 patients	Last 51 patients	
T-score at the lumbar spine	−1.52 (−1.31 to −1.72)	−3.15–2.90 to −3.4)	−2.56 (−2.18 to −2.94)	−2.11 (−1.85 to −2.38)	0.02
T-score at the femoral neck	−1.29 (−1.11 to −1.47)	−2.55 (−2.35 to −2.75)	−2.29 (−2.01 to −2.57)	−1.58 (−1.37 to −1.79)	< 0.0001
Relative time to first evaluation, years	11.7 (10.3-13.0)	8.2 (7.0-9.5)	5.7 (4.8-6.5)	14.1 (13.5-14.7)	
Sex, F/M, n (%)	30/19 (61/39)	23/30 (43/57)	24/27 (47/53)	29/22 (57/43)	
Age, years	27.7 (25.6-29.9)	28.4 (26.6-30.3)	28.0 (26.1-29.8)	28.3 (26.2-30.4)	
BMI, kg/m^2	18.1 (17.6-18.6)	17.4 (16.5-18.3)	17.0 (16.6-17.4)	18.5 (17.6-19.4)	0.001
FEV_1, % predicted	26 (24-28)	25 (22-27)	0.9 (0.7-0.9)	1.2 (0.5-1.8)	
6MWD, m	367 (336-398)	339 (301-378)	332 (300-366)	376 (340-413)	0.04
CF exacerbation in the previous year	4.4 (4.2-4.7)	4.3 (3.9-4.6)	4.3 (4.0-4.5)	4.5 (4.1-4.8)	
Prednisone use, no/yes, n (%)	37/12 (76/23)	29/21[b] (58/42)	32/16[b] (63/37)	34/17 (67/33)	
Inhaled corticosteroid use, no/yes, n (%)	28/21 (57/43)	23/27[b] (46/54)	23/25[b] (45/55)	28/23 (55/45)	
Vitamin D supplementation, no/yes, n (%)	22/27 (45/55)	27/23[b] (54/46)	33/15[b] (65/35)	16/35 (31/69)	< 0.001
Bisphosphonate therapy, no/yes, n (%)	46/3 (94/6)	42/8[b] (84/16)	46/2[b] (90/10)	42/9 (82/18)	0.05
CFRD, no/yes, n (%)	12/37 (24/76)	22/31 (42/58)	23/28 (45/55)	11/40 (22/78)	
Exocrine pancreatic insufficiency, no/yes, n (%)	46/3 (94/6)	51/2 (96/4)	47/4 (92/8)	50/1 (98/2)	
CFTR genotype, n (%)[c]					
Unknown	7 (14)	11 (21)	15 (29)	3 (6)	
Known	42 (86)	42 (79)	36 (71)	48 (94)	
Severe/Severe	25 (60)	26 (62)	20 (55)	29 (60)	
Severe/Mild	11 (26)	15 (36)	15 (42)	13 (27)	
Mild/Mild	6 (14)	1 (2)	1 (3)	6 (13)	
Estimated 5-year survival, %[d]	30 (27-34)	30 (27-34)	31 (27-35)	30 (26-33)	

BMI: body mass index; 6MWD: six-minute walk distance; CF: cystic fibrosis; CFRD: CF-related diabetes mellitus; and *CFTR: cystic fibrosis transmembrane conductance regulator*. [a]Values expressed as mean (95% CI), except where otherwise indicated. [b]Medication unknown in 3 patients. [c]Severe: class I-III mutations; and mild: class IV-VI mutations. [d]In accordance with Liou et al.[13]

With regard to *CFTR* mutation status (severe vs. mild mutations), no differences were found between the two regarding BMD.

As can be seen in Table 2, comparisons were made between CF patients evaluated for LTx in the 1992-2003 period (n = 51) and those evaluated for LTx in the 2004-2010 period (n = 51). Osteoporosis was much more common in the earlier era (n = 34; 65% vs. n = 19; 36.5%), whereas osteopenia was more common in the later era (n = 14; 27% vs. n = 27; 52%). In addition, the 51 patients evaluated in the later era had a higher BMI (18.5 kg/m^2 vs. 17 kg/m^2; p = 0.007). Furthermore, vitamin D supplementation and bisphosphonate therapy were more common in the later era than in the earlier era (n = 35; 67% vs. n = 15; 29% and n = 9; 17.3% vs. n = 2; 4%, respectively). Moreover, CFRD was more frequently diagnosed (and subsequently treated with insulin) in the later era (n = 40; 77% vs. n = 28; 54%).

In the multivariate analysis, the overall prevalence of osteoporosis was lower in the later era (OR = 0.88; 95% CI: 0.80-0.96; p = 0.005), as was the prevalence of osteoporosis at the femoral neck (OR = 0.76; 95% CI: 0.63-0.92; p = 0.05). A high FEV_1% was found to be a negative predictor of femoral neck osteoporosis (OR = 0.88; 95% CI: 0.79-0.98; p = 0.03). Males were more likely to have osteoporosis at the lumbar spine than were females (OR = 2.68; 95% CI: 1.13-6.35; p = 0.03). A low BMI was found to be a positive predictor of osteoporosis (OR = 0.75; 95% CI: 0.58-0.98; p = 0.003) and lumbar spine osteoporosis (OR = 0.70; 95% CI: 0.54-0.91; p = 0.007). Mean T-scores at the

Table 3. Biochemical parameters in the cystic fibrosis patients included in the study, by osteoporosis status (i.e., with or without osteoporosis).[a]

Parameter	All	Without osteoporosis	With osteoporosis	p	Normal range
CRP, mg/L	33 (26-40)	31 (19-44)	34 (25-42)		< 5
Creatinine, µmol/L	67 (64-70)	65 (61-68)	69 (65-73)		62-106
GFR, mL/min/1.73 km^2	92 (88-96)	95 (90-100)	90 (84-96)		
Albumin, g/L	36 (35-38)	37 (35-40)	35 (34-37)		40-49
HbA1c, %	6.7 (6.5-6.9)	6.7 (6.4-6.9)	6.6 (6.3-7.0)		4.8-5.9
Fasting glucose, mmol/L	6.5 (5.8-7.2)	6.6 (5.6-6.7)	6.8 (5.6-8.0)		< 5.6
Calcium (albumin-corrected), mmol/L	2.36 (2.32-2.40)	2.33 (2.26-2.40)	2.39 (2.36-2.43)		2.09-2.54
Phosphate, mmol/L	1.05 (1.01-1.10)	1.02 (0.95-1.09)	1.08 (1.02-1.14)		0.87-1.45
Alkaline phosphatase, U/L	139 (119-158)	138 (11-164)	140 (11-168)		40-129
Bone alkaline phosphatase, µg/L (n = 83)	15.7 (13.7-17.7)	15.1 (12.7-17.6)	16.4 (13.1-19.6)		3.7-21.1
25(OH)D, µg/L (n = 85)	21 (18-23)	21 (18-25)	20 (16-24)		10-42
25(OH)D < 30 µg/L, no/yes, n (%)	22/63 (26/74)	11/34 (24/76)	11/29 (28/72)		
PTH, ng/L (n = 84)	50 (46-61)	50 (40-59)	51 (31-71)		15-65
PTH > 65 ng/L, no/yes, n (%)	73/11 (87/13)	40/4 (91/9)	33/7 (83/17)		
Osteocalcin, ng/L (n = 30)	4.3 (3.5-5.0)	4.6 (3.3-5.9)	4.0 (3.1-5.0)		2.4-10.0
Testosterone (in males), nmol/L (n = 34)	13.6 (11.3-15.9)	15.8 (12.3-19.3)	11.7 (8.6-14.8)		7.57-31.4
Estradiol (in females), pmol/L (n = 39)	189 (129-250)	189 (95-283)	190 (110-270)		
Urinary calcium/creatinine (n = 78)	0.5 (0.5-0.6)	0.50 (0.39-0.61)	0.55 (0.45-0.65)		0.1-0.5
Urinary calcium/creatinine > 0.5, no/yes, n (%)	46/32 (59/41)	20/16 (56/44)	12/29 (29/71)	0.04	
Urinary deoxypyridinoline/creatinine (n = 85)	8.0 (7.0-9.0)	7.7 (6.3-9.1)	8.4 (6.8-9.9)		2.5-5.0
Urinary deoxypyridinoline/creatinine > 5.0, no/yes, n (%)	23/62 (27/73)	11/33 (25/75)	12/29 (29/71)		
Urinary creatinine/24 h, mmol (n = 90)	8.7 (8.0-9.4)	9.0 (8.1-9.9)	8.5 (7.5-9.5)		

CRP: C-reactive protein; GFR: glomerular filtration rate (as calculated by the Cockcroft and Gault equation); HbA1c: hemoglobin A1c; 25(OH)D: 25-hydroxyvitamin D; and PTH: parathyroid hormone. [a]Values expressed as mean (95% CI), except where otherwise indicated.

femoral neck were higher in the patients with CFRD than in those without CFRD (−1.73; 95% CI: −1.74 to −2.10 vs. −2.30; 95% CI: −1.90 to −2.69; p = 0.003; OR = 0.13; 95% CI: 0.02-0.67; p = 0.02).

DISCUSSION

Low BMD is a common comorbidity in CF patients,[16] affecting half of our cohort. This result is consistent with those of other studies[2,10,17] and shows the high prevalence of bone disease in CF patients (and, in our particular cohort, in CF patients with end-stage lung disease undergoing LTx evaluation). Osteoporosis (particularly lumbar spine osteoporosis) was found to be more common in male CF patients than in female CF patients, as reported elsewhere.[18]

CF patients with end-stage lung disease are at a high risk of low BMD, and numerous cross-sectional studies have found a number of factors associated with low BMD, including lung function, BMI, and use of corticosteroids.[4-6,8,19-21] With regard to age, there are conflicting results.[2,3,6,17,19] In our cohort, the BMI was found to have a significant impact on BMD (particularly in patients evaluated later in the study period and at the femoral neck). However, no correlation was found between age and low BMD. Given that the BMI range was rather narrow in our cohort, this seems quite remarkable. Because we did not perform detailed body composition analysis, we were unable to determine whether there was a relationship between BMD and skeletal muscle mass or between BMD and fat mass. Decreased physical capacity[4,22] and recurrent infections[10,23] are other known contributors to low BMD. In our cohort, neither exercise testing (6MWD) nor exacerbation frequency in the year before LTx evaluation correlated with low BMD. In addition, no correlation was found between low BMD and biochemical parameters. Vitamin D deficiency reflects malnutrition, affecting calcium homeostasis and bone turnover,[16] being a common finding in patients with CF. Several studies have shown that 25(OH)D is low in patients with CF, regardless of age. This is due to malabsorption, insufficient production of vitamin D in the skin (which is due to decreased exposure to sunlight as a result of lower levels of outdoor physical activity), lower amount of body fat for storage, decreased quantities of vitamin D-binding protein with a shorter half-life, and recurrent hospitalizations.[24] Vitamin D deficiency can result in secondary hyperparathyroidism, and high PTH levels can be associated with low BMD in patients with CF. West et al.[25] suggested that PTH is a more sensitive predictor of CFBD in CF patients than is 25(OH)D. Although the majority of our patients showed 25(OH)D levels of < 30 µg/L, there was no correlation of 25(OH)D with BMD or low BMD. In addition, there was no association of PTH levels with

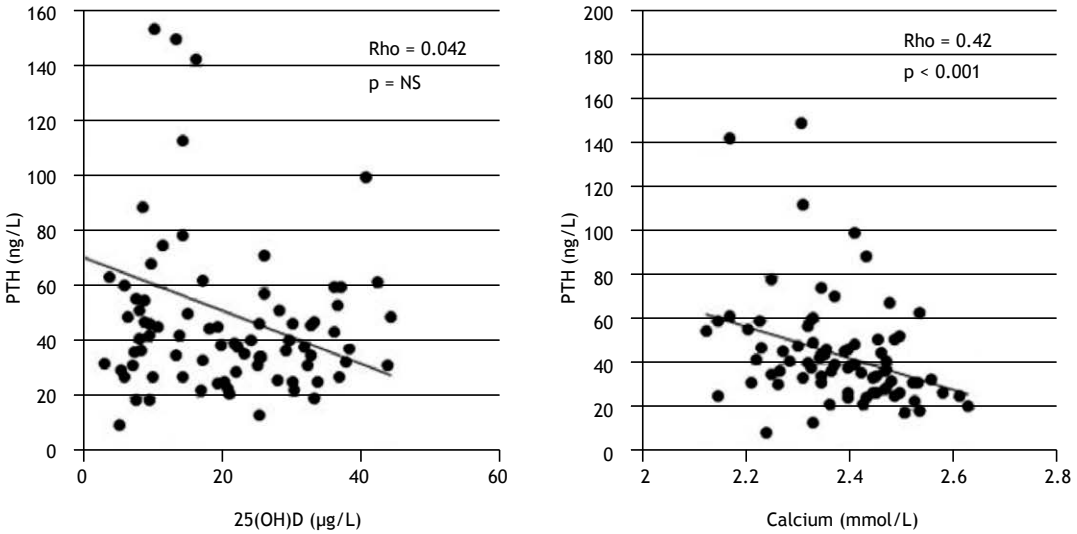

Figure 2. Spearman's correlation of serum parathyroid hormone (PTH) levels with serum 25-hydroxyvitamin D (25(OH)D) and (albumin-corrected) calcium levels. NS: not significant.

25(OH)D levels or low BMD in our patient cohort, a finding that is consistent with those of Flohr et al.[5] It is of note that secondary hyperparathyroidism was found in only 13 patients in our cohort (PTH levels > 65 ng/L). Neither decreased renal function nor low 25(OH)D levels led to increased PTH levels in the majority of our patients. In addition, PTH was found to be an inadequate parameter to detect or monitor CFBD; PTH levels did not reflect vitamin D deficiency in CF patients with end-stage lung disease and a high CFBD prevalence. However, the negative correlation between serum levels of albumin-corrected calcium and PTH was striking and highly significant. Almost 10% of the patients had borderline or elevated serum levels of albumin-corrected calcium; none had primary hyperparathyroidism. Osteocalcin, a serum marker of osteoblast activity, has been shown to correlate with bone loss.[26] Changes in bone turnover with increased bone resorption and altered bone formation have been described elsewhere.[16,27,28] However, we found no correlation of osteocalcin or deoxypyridinoline with BMD, having found only a borderline significant correlation with calciuria (as assessed in a fasting spot urine sample). Male hypogonadism has been shown to be associated with CFBD and vertebral fractures.[29,30] Although the prevalence of low BMD was higher in males than in females in our cohort, we found no correlation between testosterone and BMD.

Experimental studies have shown that *CFTR*-null mice exhibit severe osteopenia.[31] In a cross-sectional study including 88 adult patients with CF, it was reported that BMD at the lumbar spine and femoral neck is significantly lower in Phe508del homozygous or heterozygous patients than in patients without the ΔF508 mutation.[17] Aris et al.[32] speculated that *CFTR* mutations can provide a genetic link, directly influencing bone cell function. In addition, the CFTR protein has recently been shown to be expressed in human bone cells, playing an important role in the production of osteoprotegerin and prostaglandin E2, both of which are key factors in bone formation and regeneration.[33-35] Jacquot et al. tested a CFTR corrector (miglustat) in a Phe508del mutant CF mouse model, showing normalized bone volume and improved bone formation[11] and raising the question of whether CFTR-targeted drugs can act directly on bone cells. In the present study, we found no correlation between the Phe508del mutation and CFBD. Although CFTR is expressed in bone tissue and therefore CF mutation status can theoretically influence bone mass density, our data clearly demonstrate that, in patients with end-stage lung disease, the lung disease itself and pancreatic insufficiency (leading to a catabolic metabolism) have in general a much broader indirect impact on bone health than does *CFTR* mutation status.

In the present study, the frequency of low BMD at the time of LTx evaluation decreased over time. Low BMD was found to be much more common in the earlier study period than in the later study period, a finding that is consistent with those of other studies.[17,36,37] Although this reduction in the incidence of low BMD was more pronounced at the femoral neck than at the lumbar spine, the latter became more severely affected over time than did the former. The patients who were evaluated for LTx later in the study period had a significantly higher BMI. In addition, vitamin D supplementation (alone or in combination with bisphosphonate therapy) was more common in those patients, whereas systemic corticosteroid therapy was less common. Accordingly, 25(OH)D levels tended to be higher in those patients. In addition, because CFRD was more frequently diagnosed in the later era than in the earlier era, insulin treatment was more common among the patients who were evaluated for LTx later in the study period than among those who were evaluated for LTx earlier in the study period, a finding that is consistent with those of another study.[38] It is of note that BMD at the femoral neck was found to be

significantly higher in patients with CFRD. Our findings are inconsistent with those of a recent study comparing patients with moderate CF evaluated in the 1995-1999 period and those evaluated in the 2011-2013 period,[39] with no significant differences in BMD or BMI between the two cohorts of patients. Overall, the current practice for patients treated at our center has clearly led to a remarkable improvement in bone health. Our results indicate that awareness of CF as a "multiorgan disease", as well as a focus on improving nutrition and treating bone disease, together with early detection of CFRD and insulin treatment (systemic corticosteroid therapy being avoided), resulted in improved health (including bone health) and comorbidities that are less severe in our cohort of patients with CF.

Our study has several strengths. Our cohort consisted of CF patients with end-stage lung disease, thoroughly evaluated for LTx by using a standardized protocol. Therefore, our study provides detailed clinical information on a unique and well-studied cohort of patients, who were well-matched for lung function, performance status (6MWD), relative time to evaluation for LTx, and estimated 5-year survival. In comparison with other studies with similar sample size, ours involved a fairly homogenous cohort of patients with regard to lung disease severity. Evaluation of patients at a single center allows direct comparison of BMD values over a long observation period (i.e., nearly two decades), given that DXA machines were calibrated accordingly.

One limitation of our study is that DXA results were reported as T-scores. Z-scores were not available for most of the patients evaluated earlier in the study period. For reasons of comparability, data on the entire cohort were reported as T-scores. Given that the study patients were in the 25- to 30-year age bracket, T-scores were not expected to result in major data distortion.

CFBD is a common comorbidity in patients with CF and can have a severe impact on health status and health-related quality of life. The development and progression of CF clinical manifestations such as CFBD are mainly determined by environmental exposure, medical treatment, and therapy adherence, as well as *CFTR* mutation status. The prevalence of low BMD in CF lung transplant candidates has decreased in recent years, indicating a better understanding of CF as a multiorgan disease and improved multidisciplinary CF care, including early screening and treatment of CF-related comorbidities. In the present study, we found no correlation between *CFTR* mutation status and CFBD. In our opinion, lung disease severity and pancreatic insufficiency have a much broader (indirect) impact on the development of CFBD than does *CFTR* mutation status per se.

Overall, we were unable to identify a biochemical parameter associated with CFBD in CF patients with end-stage lung disease (with the possible exception of fasting calciuria, reflecting net bone loss). DXA remains the only reliable diagnostic tool to evaluate CFBD, which is still a prevalent and challenging problem, especially in patients with advanced lung disease, male patients, and patients with low BMI. In the last decade, efforts have been made to prevent and treat CFBD accordingly. Our data show that our current practice in managing patients with CFBD has lead to improved bone health.

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Does everyone who quit smoking gain weight? A real-world prospective cohort study

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Study carried out in the Ambulatório de Auxílio ao Abandono do Tabagismo, Hospital São Lucas, Faculdade de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To evaluate weight changes after 12 months of biochemically confirmed smoking abstinence, comparing patients who lost weight or maintained their baseline weight with those who gained weight. **Methods:** This was a real-world prospective cohort study conducted at the Outpatient Smoking Cessation Clinic of São Lucas Hospital, in the city of Porto Alegre, Brazil, between 2010 and 2016. The patients evaluated received intensive smoking cessation counseling, focused especially on weight issues, together with pharmacotherapy, and were followed for 12 months. The baseline and final weights were measured. Continuous abstinence was confirmed by determining the concentration of exhaled carbon monoxide (eCO). **Results:** Of a total of 348 patients evaluated, 161 (46.2%) achieved continuous abstinence (eCO < 10 ppm) over the 12-month follow-up period. Of those 161 patients, 104 (64.6%) maintained their initial weight or had a weight change of no more than 5% in relation to their baseline weight, whereas the remaining 57 (35.4%) had a weight gain of more than 5%, 18 of those patients showing a > 10% increase over their baseline weight. The number needed to harm (i.e., the number of patients required in order to detect one patient with a weight increase) was calculated to be 3.6 (95% CI: 2.8-5.4). **Conclusions:** Weight gain is not necessarily associated with smoking cessation, and smokers who are motivated to quit should be informed of that fact. This information could also be useful for addressing smokers who are still undecided because of possibility of weight gain.

Keywords: Weight loss; Smoking cessation; Tobacco smoking; Treatment outcome.

INTRODUCTION

Cigarette smoking continues to be the leading preventable cause of death in most countries.[1] It is associated with high morbidity rates and generates significantly high financial costs for the health care system.[2] Promoting smoking cessation is an important strategy to reduce the morbidity and mortality associated with smoking-related diseases. In Brazil, smoking is also a major public health problem, although there is a major trend toward a decrease in the proportion of smokers. Recent data show that the prevalence of smoking among individuals ≥ 18 years of age decreased from 15.6% in 2006 to 10.8% in 2015 ($p < 0.05$), corresponding to a 30.7% reduction.[3]

The inverse relationship between body weight and smoking is well recognized.[4-6] Smokers typically have a lower body weight than do nonsmokers.[7,8] Reduced food intake in smokers has been attributed to various mechanisms[7,9,10]: increased stimulation of the adrenergic system; lipolysis and thermogenesis secondary to an increased basal metabolic rate; increased energy expenditure; and nicotine-induced appetite suppression. There is also evidence that some additives employed in the industrial production of the cigarettes are appetite suppressants, such as tartaric acid and 2-acetylpyridine.[11] Conversely, smoking cessation is associated with weight gain,[10] and former smokers usually weigh more than do current smokers and never smokers.[5,12-14] When an individual quits smoking, the aforementioned mechanisms cease to operate, leading to an increase in body weight. A low socioeconomic status (SES) is also a contributing factor for weight gain. Currently, most smokers belong to a lower SES, engage in less physical activity, and have a high-calorie/high-fat diet. The increase in caloric intake is probably responsible for the greater proportional weight gain seen during the first 3 months after smoking cessation.[10] In addition, former smokers seek oral rewards through the consumption of foods with high sugar and fat content. There is also a rapid recovery of the senses of smell and taste, which encourages food intake.[11]

There is evidence that a considerable proportion of smokers gain weight when they quit smoking.[8,15-17] Approximately 50% of women and 26% of men state that their main concern in quitting smoking is weight gain, which is also a major risk factor for relapse.[18] The significant proportion of former smokers who maintain their original weight or show no more than 5% variation in relation to their baseline weight is not usually emphasized during the counseling of smokers who are about to initiate an attempt to stop smoking.

The aim of this study was to assess weight changes during the smoking cessation process and to identify the factors involved in such changes. We had a special

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interest in the subgroup of patients that maintained their weight or showed a variation of no more than 5% in relation to their baseline weight.[19] We also calculated the number needed to harm (NNH), which, for the purposes of the present study, was the number of patients required in order to identify one patient with a clinically relevant weight gain in relation to the baseline weight among the smokers who succeeded in quitting smoking.

METHODS

This was a prospective cohort study of smokers who sought treatment at the Outpatient Smoking Cessation Clinic of Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul (HSL-PUCRS, São Lucas Hospital of the Pontifical Catholic University of Rio Grande do Sul), in the city of Porto Alegre, Brazil. The screening period was from June 2010 to June 2016.

The inclusion criteria were being a current smoker, having a ≥ 10 pack-year smoking history, being motivated to quit smoking, and not having been under treatment for smoking cessation in the last 6 months. The exclusion criteria were having a severe clinical or psychiatric illness, including self-reported alcohol or illicit drug abuse, as well as being illiterate, being pregnant, and breastfeeding.

The study was approved by the HSL-PUCRS Scientific and Ethics Committee and is in compliance with the Brazilian regulatory guidelines for research involving human beings (National Health Council Resolution no. 466/12). All participants gave written informed consent.

The HSL-PUCRS smoking cessation program is a 12-month program and is representative of the daily clinical practice in smoking cessation treatment in Brazil. The physicians involved in the study were responsible for allocating the patients to each of the pharmacological treatment arms of the study: no pharmacological treatment, bupropion, nortriptyline, nicotine replacement therapy, and varenicline. To that end, the physicians considered the level of nicotine dependence, as determined with the Fagerström Test for Nicotine Dependence (FTND); tolerance to drugs in any previous smoking cessation treatments; patient preference for a given drug; and the financial ability of the patient to acquire the medication proposed, given that patients did not receive the medications for free. All patients received the same regimen of counseling. The program consisted of an initial medical interview, in which the patient completed a standardized questionnaire on smoking history and the level of motivation to quit. The physician then augmented the records with data regarding the general medical history, physical examination findings, baseline body weight, respiratory symptoms, and use of medications for the treatment of comorbidities. The level of nicotine dependence was then assessed with the FTND, which classifies it as low (FTND score ≤ 3), medium (FTND score of 4-7), or high (FTND score ≥ 8).[20] The concentration of exhaled carbon monoxide (eCO) was measured with a portable monoximeter (MicroCO; Micro Medical Limited, Rochester, England). Finally, the patient, the physician, and a nurse collectively agreed upon a quit day, typically scheduled for 8-9 days after the initial assessment. During the first three months of treatment, the patients attended individual treatment sessions, 15 days apart, all conducted by the same physician. After this initial period, the patients returned once a month until completing 12 months of abstinence. At all visits, the patients reported on their smoking habits and the eCO level was determined in order to confirm the smoking status. There were also visits with a trained nurse, specifically related to preventing weight change and developing strategies to cope with this problem. Withdrawal symptoms were also fully discussed in all sessions. The last follow-up visit was at 12 months of continuous abstinence, at which point the final weight was recorded. Body weight was always determined with the same scale (Filizola eletrônica digital; Industria Filizola, São Paulo, Brazil), calibrated as recommended by the manufacturer.

Successful treatment was defined as continuous abstinence (eCO < 10 ppm at all visits). Subjects who discontinued treatment or were lost to follow-up were classified as cases of treatment failure and were not included in the analysis. Any patient who did not attend a scheduled appointment received a phone call from the outpatient clinic, as a routine procedure.

For assessing outcomes, we stratified the patients into two groups, according to changes in body weight: NoChange (weight unchanged or variation of no more than 5% in relation to the baseline weight); and Change (weight gain of more than 5%). Variations in body weight greater than 5% were considered clinically relevant.[19]

We described continuous variables as means ± standard deviations when the data distribution was normal and as medians and interquartile ranges when it was not. We described categorical variables as absolute and relative frequencies. We used the Student's t-test to compare means and the nonparametric Mann-Whitney test to compare medians. For categorical data comparisons, we used the chi-square test or Fisher's exact test.

To evaluate weight change during the follow-up period, we used a Poisson regression model with a robust standard error to estimate relative risk, calculating the corresponding 95% confidence intervals and adjusting for several potential confounders. In addition, to determine the magnitude of the impact that smoking cessation had on weight gain, we calculated the NNH and the corresponding 95% confidence interval. The level of significance was set at $p < 0.05$. Data were analyzed with the SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

We screened 450 smokers, of whom 102 were excluded (Figure 1). Therefore, the final study sample

comprised 348 patients, 161 (46.3%) of whom were abstinent throughout the 12-month follow-up period (Figure 1).

Table 1 shows the characteristics of the patients evaluated, by outcome (success vs. failure in quitting smoking) and weight-change group (NoChange vs. Change). To maintain the numbers of patients in both groups, we used a cut-off age of 50 years, rather than the traditional 60 years. The cut-off age of 50 years has been used previously.[21] Among the 161 patients in whom the treatment was successful, 104 (64.6%) were in the NoChange group and 57 (35.4%) were in the Change group. Among the 187 patients in whom the treatment failed, 172 (92.0%) were in the NoChange group and 15 (8.0%) were in the Change group.

Among the patients in whom the treatment was successful, the baseline body weight was higher in the NoChange group patients than in the Change group patients, there being, as expected, less weight gain in the former group ($p < 0.001$ for both). In general, there was a weak correlation between being younger and being in the NoChange group ($p = 0.058$). Among the patients in whom the treatment failed, those in the NoChange group were significantly younger than were those in the Change group, as well as showing significantly less weight gain ($p = 0.05$ for both). We found no significant differences between the two groups regarding any of the other characteristics evaluated. As can be seen in Table 2, the patients were also grouped into seven categories, according to the percent weight change in relation to the baseline weight. Table 2 also shows the distribution of the percent weight change from the baseline weight by outcome. We detected significant differences between the two outcomes only for categories 3, 4, 6, and 7.

Table 3 demonstrates the risk factors for Change group patients, in univariate analysis and multivariate Poisson regression (adjusted for gender, age, level of nicotine dependence, pharmacological treatment received, number of clinical visits attended, and baseline body weight). None of the factors evaluated were found to confer significant risk for or protection against a > 5% weight gain in relation to the baseline weight. Figure 2 shows the risk and protective factors in a forest plot. The NNH for a > 5% weight gain in relation to the baseline weight was 3.6 (95% CI: 2.8-5.4).

DISCUSSION

In this study, the majority of the patients who achieved continuous smoking abstinence after quitting smoking had no significant weight changes or maintained their initial weight. Although many smokers gain weight after quitting smoking, the weight gain is usually minimal,[5,12,22] as we found in our sample. Therefore, the widespread notion in the lay population and among some health professionals that smoking cessation is necessarily associated with weight gain is not entirely true.

Aubin et al.[12] found that quitting smoking was associated with a mean weight gain of 4.7 kg at 12 months after smoking cessation, 13% of the abstinent smokers having gained more than 10 kg. However, a significant proportion of the former smokers evaluated in that study actually lost weight. Tian et al.[23] assessed data from 63,403 individuals who quit smoking, evaluating 388,432 current smokers as a control group. The former smokers had a mean weight gain of 4.10 kg (95% CI: 2.69-5.51), which was significantly greater than that observed in the current smokers ($p < 0.001$).

Of the 187 patients in whom the treatment failed in the present study, 172 (92.0%) patients had a weight change < 5% in relation to the baseline weight The lack of relevant changes in this group might be related to the attempt to quit smoking or to the natural weight variation of the subjects during the study period.

Our findings are consistent with those of other studies in the literature. Aubin et al.[12] showed that the majority (84%) of their abstinent patients gained weight, whereas 16% lost weight. In the present study, those proportions were 78.9% and 15.5%, respectively, and 5.6% of our patients maintained their baseline weight.

It is known that some of the drugs prescribed for smoking cessation can promote weight changes.

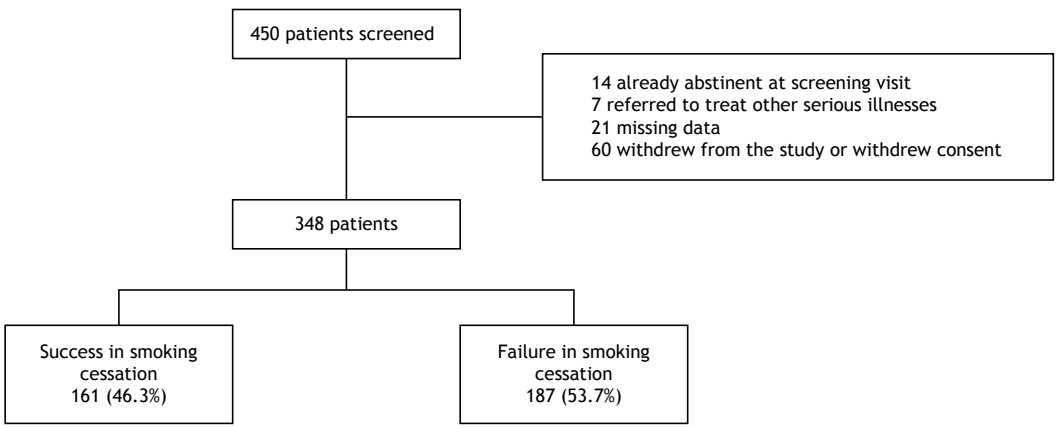

Figure 1. Flowchart of patients included in the study.

Table 1. Demographic characteristics of the sample, by treatment outcome and weight-change group.[a]

Variable	Treatment success (n = 161)			Treatment failure (n = 187)		
	NoChange (n = 104)	Change (n = 57)	p	NoChange (n = 172)	Change (n = 15)	p
Female gender	70 (67.3)	41 (71.9)	0.596	121 (70.3)	13 (86.7)	0.239
< 50 years of age	73 (70.2)	31 (54.4)	0.058	112 (65.1)	4 (26.7)	0.050
≥ 11 years of schooling	9 (9.1)	3 (5.3)	0.538	18 (10.7)	0 (0.0)	0.367
Pack-years	36 [20-50]	35 [26-57]	0.482	43 [28-60]	40 [25-66]	0.964
Treatment			0.506			0.669
Counseling only	8 (7.7)	4 (7.0)		54 (51.4)	3 (20.0)	
Counseling + BUP	78 (75.0)	38 (66.7)		85 (49.4)	8 (53.3)	
Counseling + NRT	4 (3.8)	3 (5.3)		12 (7.0)	2 (13.3)	
Counseling + NOR	5 (4.8)	7 (12.3)		17 (9.9)	2 (13.3)	
Counseling + VAR	9 (8.7)	5 (8.8)		4 (2.3)	0 (0.0)	
Nicotine dependence level (FTND)			0.324			0.246
Low	33 (31.7)	13 (22.8)		45 (26.2)	1 (6.7)	
Moderate	48 (46.2)	26 (45.6)		81 (47.1)	9 (60.0)	
High	23 (22.1)	18 (31.6)		46 (26.7)	5 (33.3)	
Baseline weight, kg	71.6 ± 15.1	66.3 ± 11.3	0.022	68.4 ± 15.3	66.9 ± 13.2	0.725
Final weight, kg	72.5 ± 15.0	72.0 ± 12.1	0.842	68.1 ± 15.4	71.5 ± 13.6	0.410
Baseline BMI, kg/m^2	26.9 ± 5.5	25.7 ± 4.4	0.172	26.6 ± 5.8	26.8 ± 3.9	0.908
Final BMI, kg/m^2	27.3 ± 5.5	27.9 ± 4.6	0.518	26.5 ± 5.8	28.6 ± 4.0	0.196
Delta BMI, kg/m^2	0.39 ± 0.57	2.21 ± 0.79	<0.001	−0.11 ± 0.65	1.85 ± 0.65	<0.001

NoChange: weight unchanged or variation of no more than 5% in relation to the baseline weight; Change: weight gain of more than 5%; BUP: bupropion; NRT: nicotine replacement therapy; NOR: nortriptyline; VAR: varenicline; FTND: Fagerström Test for Nicotine Dependence (score); and BMI: body mass index. [a]Data are presented as mean ± SD, median [interquartile range], or n (%).

Table 2. Distribution by weight-change category and treatment outcome among patients undergoing smoking cessation treatment (N = 348).

Category	% change from baseline weight	Success (n = 161) n (%)	Failure (n = 187) n (%)
1-weight loss	≥ 10.000	0 (0)	1 (0.5)
2-weight loss	9.990 to 5.000	1 (0.6)	7 (3.7)
3-weight loss	4.990 to 0.001	24 (14.9)	72 (38.5)*
4-weight maintained	0	9 (5.6)	23 (12.3)*
5-weight gain	> 0.001 to 4.990	70 (43.5)	69 (36.9)
6-weight gain	5.000 to 9.990	39 (24.2)	13 (7.0)*
7-weight gain	≥ 10.000	18 (11.2)	2 (1.1)*

*p ≤ 0.05.

Bupropion is widely used for slimming as well as for smoking cessation.[19] Although nortriptyline is associated with weight gain when used to treat depression,[24] its specific role in weight changes when used in smoking cessation treatment has not been fully tested. However, we found no significant differences among the pharmacological treatment arms in terms of weight changes. Aubin et al.[12] reported similar findings in a study comparing the use of nicotine replacement therapy, bupropion, varenicline, and no pharmacotherapy.

The factors that have been associated with weight gain after smoking cessation include male gender, a higher level of nicotine dependence, and advanced age.[22] There have also been studies showing that being < 55 years of age and having a lower SES are significant risk factors for weight gain after smoking cessation.[25] Discrepancies across studies are likely related to differences in the length of the follow-up period.

On average, smokers weigh less than do nonsmokers. The proportion of smokers who are overweight or obese in a given population is reflective of the dietary habits in the respective country or region. Many smokers are already overweight or even have class III obesity when they attempt to quit smoking. Smoking is especially common among individuals who are preparing to undergo bariatric procedures. In a previous study conducted at our facility,[7] the relationship between class III obesity and smoking was evaluated, and

Table 3. Univariate analysis and multivariate Poisson regression of risk factors associated with a weight gain of more than 5% in relation to the baseline weight among the patients in whom the treatment was successful (n = 161).

Variable	Crude RR (95% CI)	p	Adjusted RR* (95% CI)	p
Female gender	1.15 (0.65-2.06)	0.63	1.15 (0.63-2.11)	0.64
< 50 years of age	1.53 (0.91-2.58)	0.11	1.63 (0.94-2.83)	0.081
≥ 11 years of schooling	0.67 (0.21-2.13)	0.49	0.72 (0.22-2.36)	0.59
Pack-years	1.00 (0.99-1.01)	0.66	1.01 (0.99-1.02)	0.41
Comorbidities	1.15 (0.64-2.08)	0.63	1.24 (0.66-2.32)	0.51
Treatment				
Counseling	1		1	
Counseling + BUP	0.98 (0.35-2.75)	0.97	0.93 (0.33-2.62)	0.89
Counseling + NRT	1.29 (0.29-5.75)	0.74	1.36 (0.30-6.18)	0.69
Counseling + NOR	1.75 (0.51-5.98)	0.37	1.25 (0.36-4.37)	0.73
Counseling + VAR	1.07 (0.29-3.99)	0.92	0.99 (0.26-3.71)	0.98
Nicotine dependence (FTND)				
Low	1		1	
Moderate	1.24 (0.64-2.42)	0.52	1.15 (0.58-2.28)	0.69
High	1.53 (0.76-3.17)	0.23	1.49 (0.71-3.13)	0.29
Baseline weight	0.98 (0.96-1.00)	0.06	0.98 (0.96-1.01)	0.12
Baseline BMI, kg/m^2	0.97 (0.91-1.03)	0.27	0.98 (0.92-1.04)	0.41
< 24	1		1	
25-30	0.77 (0.43-1.41)	0.40	0.97 (0.51-1.84)	0.93
> 30	0.66 (0.30-1.47)	0.31	0.70 (0.31-1.61)	0.40
Medical visits attended (n)	1.08 (1.01-1.15)	0.02	1.05 (0.88-1.26)	0.56

RR: relative risk; FTND: Fagerström Test for Nicotine Dependence (score); BUP: bupropion; NRT: nicotine replacement therapy; NOR: nortriptyline; VAR: varenicline; and BMI: body mass index. *Adjusted for gender, age, level of nicotine dependence (FTND score), treatment, number of visits attended, and baseline weight.

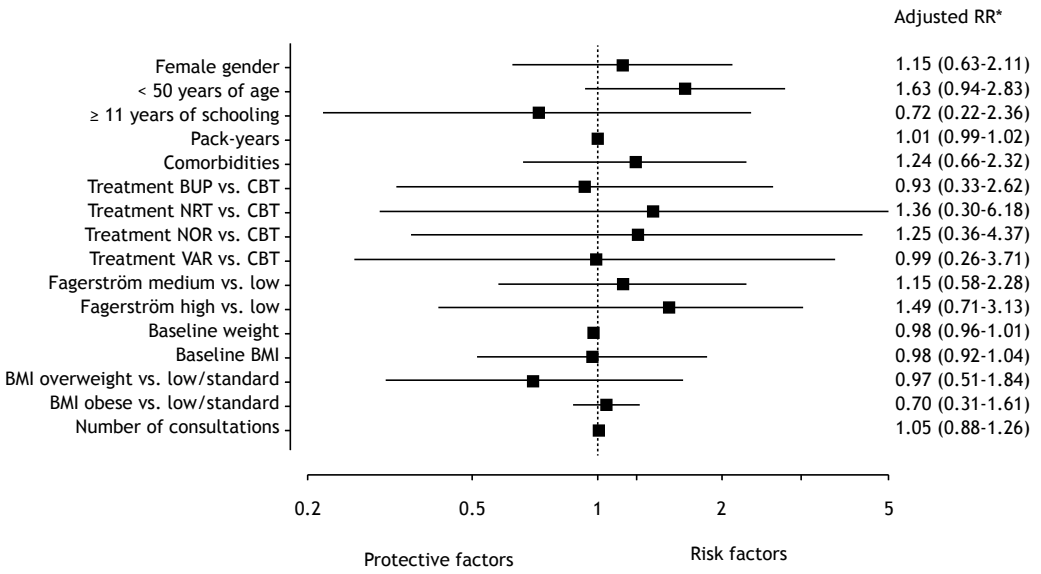

Figure 2. Forest plot of risk and protective factors for significant weight gain, adjusted for gender, age, and level of nicotine dependence (Fagerström Test of Nicotine Dependence), treatment, and follow-up. RR: relative risk; BUP: bupropion; CBT: cognitive behavioral therapy; NRT: nicotine replacement therapy; NOR: nortriptyline; VAR: varenicline; and BMI: body mass index. *Logistic regression model adjusted for gender, age, level of nicotine dependence (Fagerström Test for Nicotine Dependence score), treatment, and follow-up.

patients with class III obesity were found to be two times more likely to be a smoker than were those with lower BMIs.[7] Those findings might be a consequence of various overlapping risk behaviors, because smokers are typically less physically active and prefer a less healthy diet, as well as consuming greater quantities of alcohol, in comparison with their non-smoking counterparts. In a subsequent study, involving 536 individuals with class III obesity, smoking was found to correlate positively with BMI, waist circumference, and percentage of body fat among the male patients with class III obesity.[9]

Although our findings confirm previously published results, our study adds some innovative information. To our knowledge, this is the first paper to use NNH calculation, a simple technique, to determine the number of treated patients needed in order to detect one with a significant weight change. The fact that we calculated an NNH of 3.6 means that for every 3.6 people treated, only one will show a weight gain of more than 5%, whereas 2.4 will maintain their baseline weight or even lose a small proportion. The dissemination of our findings could be useful for encouraging smokers to quit. Patients should be informed that weight gain is not a significant problem in the majority of the cases.[24] The benefits of quitting smoking outweigh any potential risks related to weight gain. Patients should also be informed that systemic arterial hypertension and type 2 diabetes mellitus, as collateral effects of weight gain—often mentioned by patients as major concerns—are uncommon, and that the benefits of quitting by far offset the consequences of weight gain related to smoking cessation.[26,27] Nevertheless, in our sample, 11% of the patients in whom treatment success was achieved showed weight gains that could be harmful to their health (more than 10% in relation to the baseline weight). Of the patients in whom the treatment failed, only 1.1% showed such weight gains.

This study has a number of strengths. Because we employed a real-world prospective cohort design, our findings reflect the routine scenario of smoking cessation treatment at outpatient clinics in Brazil. Our sample is representative of the patients treated via the Brazilian Unified Health Care System. Another positive point is that we managed to perform biochemical verification of smoking withdrawal in all cases, despite the long follow-up period. All patients had to purchase their own medication, which could be an indicator of good adherence to the treatment and of a strong motivation to try to complete the task of quitting smoking. Another strength is that we expressed weight change as a percentage of the baseline weight, rather than as an absolute value. This innovative strategy was implemented in order to prevent erroneous interpretations. To avoid measurement errors,[14,28] body weights were verified by a health care professional.

Our study has some limitations. The high proportion of patients treated with bupropion could have introduced a bias. However, after adjusting for several factors, we found that treatment with bupropion had no significant influence on the results. In terms of the treatment received, the patients in whom treatment success was achieved were comparable to those in whom the treatment failed. However, when we stratified the patients by weight-change group (NoChange and Change), we detected differences in the two groups that were controlled by the multivariate Poisson regression. Another limitation is that we did not evaluate possible modifications in physical activity or lifestyle. The patients might have gained weight because of lifestyle changes, such as becoming more sedentary, or might have lost weight because they started engaging in regular physical activity. In addition, patients who exercised could have increased their muscle mass, with a consequent increase in weight, which could be better evaluated by bioimpedance. Unfortunately, when we started this study, we did not have access to the equipment necessary in order to assess body composition or to determine the proportional distribution of lean and fat mass in each body segment. In the multivariate analysis, we adjusted for the possible bias of using drugs that can affect the appetite. Because this was a real-world study, the patients were not randomized to the various treatments, which could represent a bias related to patients selecting the medications on the basis of price. However, that reflects what happens in daily practice: patients do not receive medication for free. Because our findings are in keeping with those of other studies in the literature,[27,29] we are confident that these limitations did not have a significant influence on our results.

The idea that weight gain after smoking cessation can be insignificant when specific measures for weight control are taken should be widely disseminated. Health care professionals, especially those working at primary health care clinics or smoking cessation treatment centers, should use this information as a tool to emphasize to patients that, although there truly is a possibility of weight gain during smoking cessation treatment, such weight gain occurring in a non-negligible proportion of patients, a larger proportion of patients retain their baseline weight or even lose weight. Health care professionals should further explain that weight changes will not be a major problem if certain precautions are taken.[27,30,31] They should transmit to the smoker the idea that it is possible to quit smoking without a great risk of weight gain or of the specific comorbidities usually associated with obesity, such as systemic arterial hypertension and diabetes mellitus.[29] This strategy could help motivated smokers overcome barriers and encourage them to give up the habit. It could also be useful in addressing undecided smokers who are concerned about possible weight gain.

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Incidence and morphological characteristics of the reversed halo sign in patients with acute pulmonary embolism and pulmonary infarction undergoing computed tomography angiography of the pulmonary arteries

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ABSTRACT

Objective: To determine the incidence of the reversed halo sign (RHS) in patients with pulmonary infarction (PI) due to acute pulmonary embolism (PE), detected by computed tomography angiography (CTA) of the pulmonary arteries, and to describe the main morphological features of the RHS. **Methods:** We evaluated 993 CTA scans, stratified by the risk of PE, performed between January of 2010 and December of 2014. Although PE was detected in 164 scans (16.5%), three of those scans were excluded because of respiratory motion artifacts. Of the remaining 161 scans, 75 (46.6%) showed lesions consistent with PI, totaling 86 lesions. Among those lesions, the RHS was seen in 33 (38.4%, in 29 patients). **Results:** Among the 29 patients with scans showing lesions characteristic of PI with the RHS, 25 (86.2%) had a single lesion and 4 (13.8%) had two, totaling 33 lesions. In all cases, the RHS was in a subpleural location. To standardize the analysis, all images were interpreted in the axial plane. Among those 33 lesions, the RHS was in the right lower lobe in 17 (51.5%), in the left lower lobe in 10 (30.3%), in the lingula in 5 (15.2%), and in the right upper lobe in 1 (3.0%). Among those same 33 lesions, areas of low attenuation were seen in 29 (87.9%). The RHS was oval in 24 (72.7%) of the cases and round in 9 (27.3%). Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS. **Conclusions:** A diagnosis of PE should be considered when there are findings such as those described here, even in patients with nonspecific clinical symptoms.

Keywords: Pulmonary embolism; Pulmonary infarction; Computed tomography angiography.

INTRODUCTION

Acute pulmonary embolism (PE) is a major cause of morbidity and mortality, requiring early diagnosis to enable appropriate treatment. PE is the third leading cause of morbidity and mortality among acute cardiovascular diseases, and is the most common cause of death in inpatients. However, it is believed that PE was suspected in only 30% of the patients who eventually died of the disease.[1-3]

It is estimated that approximately 5 million patients present with deep vein thrombosis in the United States every year.[4,5] Of those, approximately 650,000 (13%) develop PE and 100,000 to 200,000 (15.3-30.7%) die of the disease.[4,6] Epidemiological studies on PE in Brazil are few, almost all of which were based on autopsy findings, and show that the prevalence of the disease ranges from 3.9% to 16.6%.[3]

The signs and symptoms of PE are often nonspecific, requiring a high degree of suspicion. Early diagnosis to enable the institution of appropriate treatment is essential for preventing major complications, including death. A diagnosis of PE cannot be based solely on clinical data, and imaging studies, especially computed tomography angiography (CTA) of the pulmonary arteries, play a key role in this investigation. Detection of arterial luminal filling defects by CTA is the key finding for making the diagnosis. In addition, CT allows analysis of the lung parenchyma, mediastinum, and pleural cavity, with excellent spatial resolution.

Recent studies in the literature have focused on PE-related parenchymal signs[4,7,8] that, in special situations, such as inconclusive studies, could be important for diagnosis. Balakrishnan et al.[7] identified areas of reduced attenuation within the pulmonary infarction (PI) in up to 58% of the patients. He et al.[4] used the term "internal air lucencies" to describe the sign they identified within the PI in 32% of the cases evaluated, whereas Revel et al.[8] identified central lucencies within the PI in 46% of their patients. In those studies, the findings

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described are similar to the reversed halo sign (RHS), although the RHS was not identified by the authors.

In a study published in 2012, Marchiori et al.[9] evaluated 79 cases of RHS, describing infectious and noninfectious causes, and, in 7 of those cases, the RHS was caused by PI. Subsequently, in a study published in 2013, Casullo and Semionov[10] conducted a retrospective analysis of 12 cases of PE and PI in which the RHS was detected, showing that this sign could be clinically relevant in the diagnosis of PE. Therefore, the analysis of parenchymal findings on CT may be critical in patients with silent or unsuspected PE, in patients undergoing unenhanced imaging for the investigation of nonspecific clinical symptoms, or when CTA does not achieve adequate contrast of the pulmonary arteries, which can occur in up to 3% of cases.[8]

The objective of the present study was to determine the incidence of the RHS in patients with PI due to acute PE, detected by CTA of the pulmonary arteries, and to describe the main morphological features of the RHS.

METHODS

This was a cross-sectional, retrospective, observational study of PE-protocol CTA scans of the chest performed between January of 2010 and December of 2014 in the radiology department of a private hospital in Taguatinga, Brazil. The patients, who had been clinically suspected of having PE and had been stratified by the Wells score,[11] were referred from the hospital emergency room, inpatient units, and outpatient clinics to the Radiology Department of the same hospital for dedicated PE-protocol CTA of the chest. The study was approved by the Ethics Committee of the Cardiology Institute of the Federal District of Brasília (Ruling no. 844,585).

The scans were obtained in two 16-channel multidetector CT scanners (Activion; Toshiba, Tokyo, Japan), with intravenous injection of nonionic iodinated contrast (Omnipaque 300; GE Healthcare, Chicago, IL, USA), using a contrast injection pump (Stellant D; Medrad, Warrendale, PA, USA), at a flow rate of 3-5 mL/s and a total injected volume of 100-150 mL.

Images were reconstructed in a 512 × 512 pixel matrix, with a slice thickness of 1 mm and an interslice gap of 1 mm. The lungs were assessed with window widths ranging from 1,200 to 2,000 HU and center levels ranging from −300 to −700 HU. The mediastinum was assessed with window widths ranging from 350 to 500 HU and center levels ranging from 10 to 50 HU. In addition, coronal and sagittal multiplanar reconstructions were performed.

The scans were independently reevaluated by three thoracic radiologists, and disagreements were resolved by consensus. An imaging study was considered positive if at least two radiologists agreed. The criteria used to define the CT findings were those reported in the 2010 illustrated Brazilian consensus.[12]

PI was defined as the presence of peripheral consolidations on CT, with a pleural base and little contrast uptake, in patients with CTA-confirmed PE[4,8,13]; in addition, whenever possible, its lobar/segmental location was determined according to the occluded arterial branch. Patients with PI were assessed for the presence of the RHS, defined as an area of central ground-glass opacity surrounded by a peripheral halo of crescent-shaped consolidation, forming more than three quarters of a circle, or a peripheral halo of ring-shaped consolidation, forming a complete circle.[14,15]

Each scan from a patient with CTA-confirmed PE was initially analyzed for the presence of lesions consistent with PI. Contiguous lesions were considered a single lesion for statistical purposes, and, for standardization purposes and by consensus among the examiners, positive images were interpreted only in the axial plane. Subsequently, the positive images were evaluated for the presence of lesions consistent with the RHS and due to PI, and then the following characteristics were assessed: number of lesions characteristic of PI with the RHS per patient; lobar location of the lesions; presence or absence of heterogeneous areas of low attenuation within the central ground-glass opacity, with or without reticulation, in the lesions; and presence or absence of pleural effusion in the patients with the RHS.

RESULTS

In the present study, we evaluated 993 consecutive PE-protocol CTA scans, obtained between January of 2010 and December of 2014, which were stratified by the risk of PE by the hospital medical teams. PE was detected in 164 scans (16.5%). Three of those scans were excluded from the sample because of respiratory motion artifacts that impaired the analysis of the lung parenchyma, leaving a total of 161 scans in the study sample. Of the remaining scans, 75 (46.6%) showed lesions consistent with PI, totaling 86 lesions. Among those lesions, the RHS was identified in 33 (38.4%, in 29 patients). Therefore, the RHS was detected in 18% of the patients with CTA-confirmed PE. Figure 1 shows the selection of patients.

Of the 29 patients with PI and the RHS, 22 (75.9%) were female and 7 (24.1%) were male. The mean age was 43 years and 3 months, ranging from 21 to 84 years. Patients in the fourth decade of life were most often affected (13 patients).

Of those same 29 patients, 25 (86.2%) had a single lesion consistent with the RHS and 4 (13.8%) had two (Figures 2 through 5). No more than two lesions were detected per patient in our study sample. It is of note that all lesions consistent with the RHS (n = 33) were in a subpleural location. Of those 33 lesions, 17 (51.5%) were in the right lower lobe (RLL), 10 (30.3%) were in the left lower lobe (LLL), 5 (15.2%) were in the lingula, and 1 (3.0%) was in the right upper lobe (RUL). Therefore, the RHS was in the lower lobes in 81.8% of the cases.

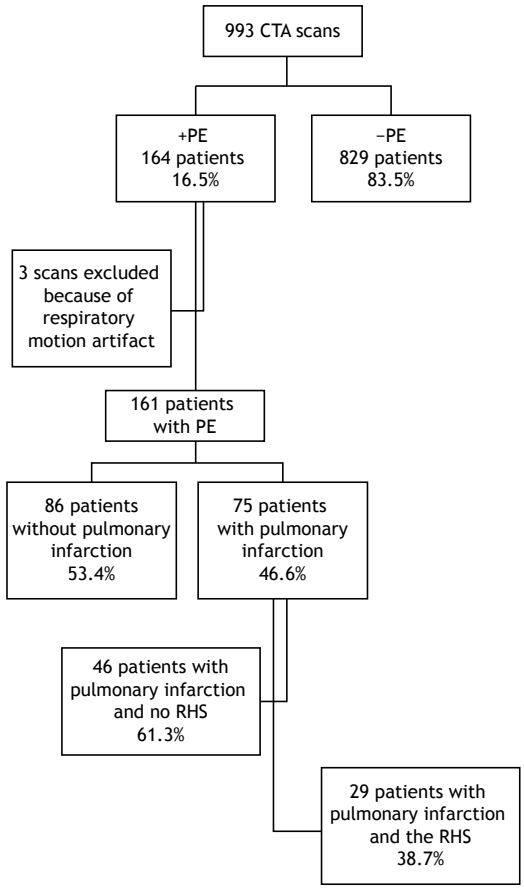

Figure 1. Patient selection process. CTA: CT angiography; PE: pulmonary embolism; and RHS: reversed halo sign.

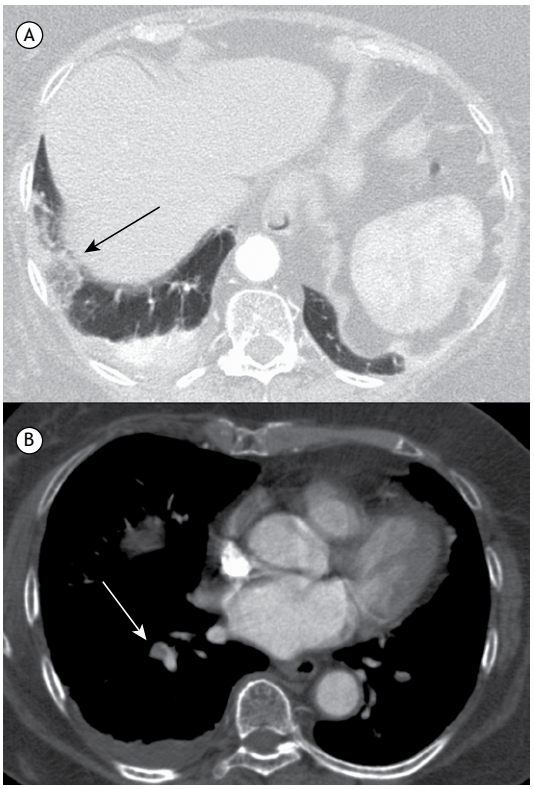

Figure 2. In A, computed tomography angiography image, with lung window settings, showing a lesion characteristic of pulmonary infarction with the reversed halo sign (black arrow) in the subpleural region of the right lower lobe, comprising heterogeneous areas of low attenuation. A small pleural effusion is also seen on this side. In B, computed tomography angiography image, with mediastinal window settings, showing a small filling defect (white arrow) at the emergence of the segmental branch that connects the right pulmonary artery to the lateral basal segment of the lower lobe.

Heterogeneous areas of low attenuation, with or without reticulation, were seen in 29 (87.9%) of the lesions characteristic of PI with the RHS; only 5 lesions (12.1%) did not show reticulation. The RHS was oval (greater diameter parallel to the pleural surface) in 24 (72.7%) of the cases and round (equivalent diameters) in 9 (27.3%). Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS.

DISCUSSION

We analyzed 993 PE-protocol CTA scans of clinically stratified patients, and PE was confirmed in 164 (16.5%). Stein et al.[16,17] analyzed 824 PE-protocol CTA scans, and PE was confirmed in 192 patients (23%), a proportion slightly higher than that found in the present study. This difference might be due to the fact that the study conducted by Stein et al.[16,17] was a prospective multicenter study conducted to validate CTA as a diagnostic method for PE, probably with better patient selection and stratification. In contrast, the present study is retrospective in nature, and the patients selected, despite having been clinically evaluated and stratified, were referred for CTA from various hospital units, such as the emergency room, inpatient units, outpatient clinics, and ICUs, by various physicians. Therefore, our inclusion criteria might not have been as stringent as those of the Stein et al. study.[17]

PI in cases of PE occurs despite the fact that the lungs have a double arterial blood supply from the pulmonary and bronchial arteries[6,18,19]; in addition, it is of note that the lung tissue is oxygenated by the alveoli.[20] PI is more common when the peripheral pulmonary artery branches are occluded,[4,20-22] because the bronchial arteries are believed to play a minor role in the parenchymal perfusion of the lung periphery.[4]

The incidence of PI in patients diagnosed with PE in the present study was 46.6%, higher than that found by He et al. (32%).[4] A comparative analysis of the two studies reveals large methodological differences. In their study, He et al.[4] analyzed 74 CTA scans that were positive for PE, whereas, in our study, we analyzed 161. In addition, the selection of positive cases in the study conducted by He et al. was based on final imaging reports, and only in cases in which the reports were positive for PE were the images assessed for PI, whereas, in the present study, positive cases were identified by studying the images from all patients who underwent PE-protocol

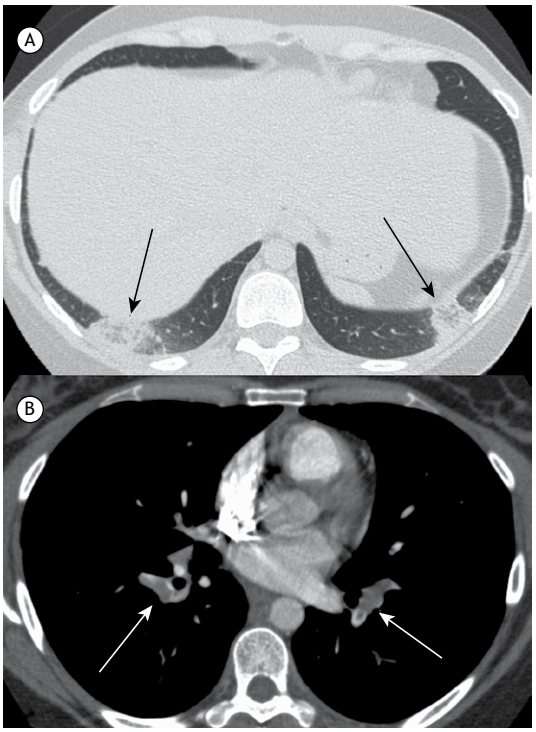

Figure 3. In A, computed tomography angiography image, with lung window settings, showing lesions characteristic of pulmonary infarction with the reversed halo sign (black arrows) in the subpleural region of the lower lobes, containing reticulation; the lesion in the right lower lobe is oval, and the one in the left lower lobe is round. In B, computed tomography angiography image, with mediastinal window settings, showing filling defects (white arrows) at the emergence of the pulmonary arteries.

CTA rather than by studying imaging reports, and there was therefore no risk of omitting images whose reports were negative for PE and might be wrong. Most patients in the study conducted by He et al.[4] (n = 45) underwent imaging in a 4-channel scanner; in the present study, all scans were performed in 16-channel scanners. In the study conducted by He et al.,[4] some of the patients were injected with contrast medium without bolus tracking or correct calculation of delay time, which may have reduced the accuracy of the diagnosis of PE; in contrast, in the present study, bolus tracking was performed in all patients. We believe that these differences had an impact on the incidence of PI, which was higher in the present study. It is also of note that the major predisposing factors for PI are left heart failure, pneumonia, septicemia, and malignancy.[4,23] In our study, all patients came from a hospital setting comprising a regional referral center for cancer. Although we could not clinically assess all of the patients included, which would go beyond the scope of the present study, we believe that, because they were hospitalized patients, they had more comorbidities and predisposing factors for PI, which would further contribute to a higher incidence of PI in the present study.

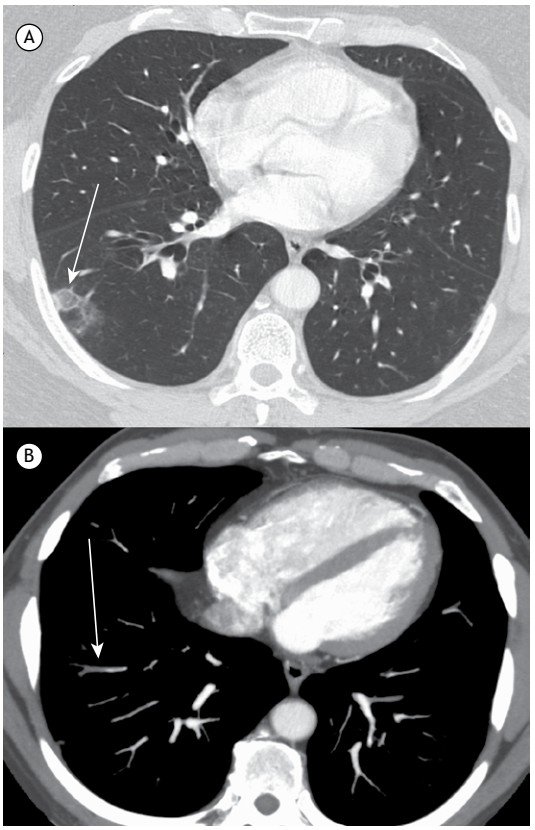

Figure 4. In A, computed tomography angiography image, with lung window settings, showing a round lesion characteristic of subpleural pulmonary infarction with the reversed halo sign (white arrow) in the right lower lobe, comprising heterogeneous areas of low attenuation and no evident reticulation. In B, computed tomography angiography image, with mediastinal window settings, showing a small filling defect (white arrow) in the segmental branch that connects the right pulmonary artery to the lower lobe.

Although the RHS is considered a finding with low specificity, the presence of nodules on the wall of or within the halo (nodular RHS) and the presence of a reticular pattern within the halo (reticular RHS) are morphological features that can narrow the differential diagnosis.[24-26] The nodular RHS is found in active granulomatous diseases, especially tuberculosis and sarcoidosis.[27] With regard to the reticular RHS, the primary diagnostic hypothesis in immunocompromised patients is that of invasive fungal diseases.[28] In immunocompetent patients, the reticular RHS usually corresponds to PI, usually secondary to thromboembolic disease.[29]

There are few studies in the literature discussing the RHS in patients with PI. However, an analysis of CT images obtained from previously published studies about the morphological features of thromboembolic PI reveal imaging patterns similar to those of the RHS,[4,7,8] although the RHS itself was not identified by the authors.

As previously mentioned, He et al.[4] used the term "internal air lucencies" to describe the sign observed

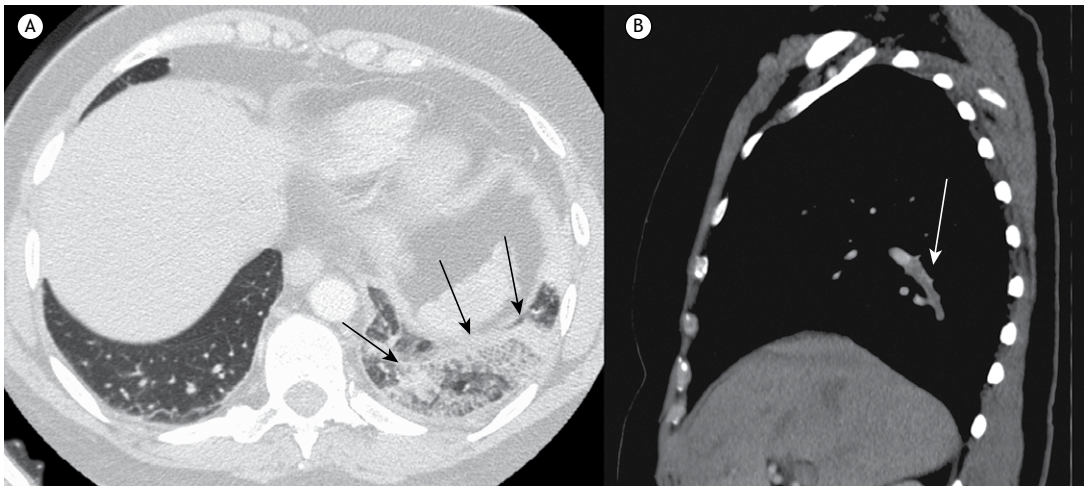

Figure 5. In A, computed tomography angiography image, with lung window settings, showing oval lesions characteristic of pulmonary infarction with the reversed halo sign (black arrows) in the subpleural region of the left lower lobe, comprising heterogeneous areas of low attenuation. In B, sagittal reconstruction, with mediastinal window settings, showing an extensive filling defect (white arrow) in the segmental branch that connects the left pulmonary artery to the posterior basal segment of the lower lobe.

in 32% of patients with PI. Revel et al.[8] described PI comprising central lucencies with peripheral consolidations in up to 46% of their patients. Balakrishnan et al.[7] reported that areas of reduced attenuation within peripheral consolidations could be seen in up to 58% of the patients with PI. In none of those three studies is there any mention of the RHS.

In the previously mentioned study published in 2012, Marchiori et al.[9] reported that the RHS was found in infectious and noninfectious diseases, and that, among the noninfectious causes, PI with imaging findings consistent with the RHS was seen in 7 cases. In the previously mentioned study published in 2013, Casullo and Semionov[10] identified the RHS in PI in a retrospective analysis of 12 cases. Those authors described the morphology, location, and number of lesions per patient, showing that this sign could have some clinical relevance in the diagnosis of PE, despite the small sample. However, the incidence and morphological features of the RHS in thromboembolic PI, as well as its true association with PE, have not been fully elucidated, and clarifying that was one of the objectives of the present study.

In the present study, we found 75 patients with PI, and, in 29 of those patients, the RHS was detected, which corresponds to approximately 39% of the patients with PI involved in the study. In those 75 patients, we found a total of 86 lesions consistent with PI, and, in 33 of those lesions, the RHS was identified, which corresponds to 38.4% of that total; in all cases, the RHS was in a subpleural location. This proportion is slightly higher than that found in the study conducted by He et al.,[4] who identified internal air lucencies in 32% of the PIs, although, as previously discussed, those authors did not use the term "RHS" to describe their findings. This proportion difference might be due to the methodologies used, because the primary objective of our study was to identify only the RHS in PI.

Morphological analysis of the PIs with the RHS revealed that the lesion was oval in 24 (72.7%) of the cases, a finding similar to what was reported by Casullo and Semionov,[10] who found this same characteristic in 71% of the cases. The oval shape was markedly predominant in that study[10] and in ours, which could contribute to the diagnosis.

Heterogeneous areas of low attenuation within the ground-glass opacity, which were possibly due to coagulation necrosis, edema, and inflammation, as discussed above, were identified in 87.9% of the cases in the present study, a proportion that is similar to that reported by Marchiori et al.[29] (94.6% of the cases), showing the importance of this morphological feature in the diagnosis of PI with the RHS.

Among the 29 patients with scans showing lesions characteristic of PI with the RHS, 25 (86.2%) had a single lesion and 4 (13.8%) had two. None of the patients had more than two lesions consistent with the RHS. In the study conducted by Casullo and Semionov,[10] 83% had a single such lesion, compared with 84.4% in the study conducted by Marchiori et al.[29]; both proportions are similar to that found in our study. Another important point is that we did not detect more than two lesions consistent with the RHS per patient, a finding also reported by Marchiori et al.[29]; this supports the notion that the finding of more than three such lesions in the same patient makes the diagnosis of PI due to PE unlikely.

Cha et al.[20] found that 53.1% of the PIs were in the RLL and 20.4% were in the LLL. In the sample studied by He et al.,[4] 73% of the PIs were in the lower lobes, 49% of which were in the RLL and 24% of which were in the LLL. Casullo and Semionov,[10] specifically evaluating the RHS in PI, found that 50%

of the lesions were in the RLL and 36% were in the LLL. Marchiori et al.[29] found that 93.2% of the imaging findings characteristic of PI with the RHS were in the lower thirds of the lungs. In the present study, we found similar results, with 17 (51.5%) of the PIs with the RHS being in the RLL and 10 (30.3%) being in the LLL. In summary, 81.8% of the lesions characteristic of PI with the RHS were detected in the lower lobes in the present study, a finding similar to what has been reported in the literature.[10,29]

Pleural effusion was seen in 21 (72.4%) of the 29 patients with PI and the RHS in the present study. In the study conducted by Casullo and Semionov,[10] there is no mention of the presence or absence of pleural effusion. In contrast, Marchiori et al.[29] reported finding pleural effusion in 64.1% of the patients with PI. The presence of pleural effusion in patients with PI could be explained by the subpleural location of the PI, accompanied by the presence of ischemia and hemorrhage, leading to pleural irritation and, consequently, to the onset of effusion. The slightly higher incidence of pleural effusion in our study might be due to the fact that our study sample consisted only of hospitalized patients, who potentially have more comorbidities.

The present study has some limitations, such as the fact that it was a retrospective observational study involving a sample of patients drawn from a single hospital and that it lacked histopathological confirmation of the PIs with the RHS. However, all patients included in the study had unequivocal CTA signs of PE, and the scans showing lesions characteristic of PI with the RHS were analyzed by three thoracic radiologists, an imaging study being considered positive if at least two examiners agreed. In addition, obtaining histopathological material from patients with PE with signs of PI is ethically unacceptable in daily practice. However, the examiners agreed that the images analyzed were consistent with PI.

In summary, the RHS was detected in 29 (18%) of the 161 patients with CTA-confirmed PE. Most (86.2%) of the patients with PI and the RHS had a single lesion, although 13.8% had two. None of the patients had more than two lesions. The RHS was oval in 72.7% of the cases, and reticulation within the ground-glass opacity was present in 87.9%. We found a higher incidence of lesions characteristic of PI with the RHS in the lower lobes (81.8%), and, in all cases, the lesions were in a subpleural location. In conclusion, attending physicians should consider a diagnosis of PE when there are incidental findings such as those described here, even in patients with nonspecific clinical symptoms.

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ORIGINAL ARTICLE

Is a low level of education a limiting factor for asthma control in a population with access to pulmonologists and to treatment?

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ABSTRACT

Objective: To determine whether a low level of education is a risk factor for uncontrolled asthma in a population of patients who have access to pulmonologists and to treatment. **Methods:** This was a cross-sectional study involving outpatients > 10 years of age diagnosed with asthma who were followed by a pulmonologist for at least 3 months in the city of Jundiai, located in the state of São Paulo, Brazil. The patients completed a questionnaire specifically designed for this study, the 6-item Asthma Control Questionnaire (to assess the control of asthma symptoms), and a questionnaire designed to assess treatment adherence. Patients underwent spirometry, and patient inhaler technique was assessed. **Results:** 358 patients were enrolled in the study. Level of education was not considered a risk factor for uncontrolled asthma symptoms (OR = 0.99; 95% CI: 0.94-1.05), spirometry findings consistent with obstructive lung disease (OR = 1.00; 95% CI: 0.99-1.01), uncontrolled asthma (OR = 1.03; 95% CI: 0.95-1.10), or the need for moderate/high doses of inhaled medication (OR = 0.99; 95% CI: 0.94-1.06). The number of years of schooling was similar between the patients in whom treatment adherence was good and those in whom it was poor (p = 0.08), as well as between those who demonstrated proper inhaler technique and those who did not (p = 0.41). **Conclusions:** Among asthma patients with access to pulmonologists and to treatment, a low level of education does not appear to be a limiting factor for adequate asthma control.

Keywords: Asthma; Educational status; Spirometry; Treatment adherence and compliance.

INTRODUCTION

Education affects various aspects of life, including health. In adults with a clinical diagnosis of asthma, a higher level of education is associated with greater knowledge about the disease and greater skill in the use of asthma inhalers,[1] which could facilitate the control of respiratory symptoms. Therefore, it is possible that patients with lower levels of education need more attention from the physician in order to achieve adequate asthma control.

Previous studies have shown that patients with asthma who have lower levels of education also have more respiratory symptoms.[2-4] However, such patients often lack access to physicians, to treatment, or to both.[5] Therefore, in those studies, the higher frequency of respiratory symptoms identified in individuals with low levels of education may have been a consequence of a lack of access to physicians or to treatment, rather than of the level of education per se. It is important to gain a better understanding of the relationship between level of education and asthma control in order to identify the characteristics of patients who are susceptible to uncontrolled asthma, especially in the current landscape. Although some advances have been made,[6,7] most patients with asthma still have not achieved adequate control of their symptoms.[8]

The hypothesis of the present study was that a low level of education would not be a limiting factor for the adequate control of asthma in a population of patients who have access to pulmonologists and to treatment, and the main objective was to test that hypothesis. A secondary objective was to assess whether level of education would be associated with variables that contribute to asthma control, such as treatment adherence and correct inhaler technique.

METHODS

Study population

We screened consecutive patients at the municipal outpatient pulmonology clinics in the city of Jundiai, located

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in the state of São Paulo, Brazil, and at the outpatient pulmonology clinics of the largest private hospital in the same city. All of the patients had access to a pulmonologist and to free asthma therapy, with inhaled corticosteroids, as well as with long- and short-acting β_2 agonists. The medication is provided via one of two federal programs—the Special Medications Program and the Popular Pharmacy Program—or by pharmacies of the primary health care clinics operated by the city of Jundiai. All of the patients included in the study were screened between August and December of 2017.

Inclusion and exclusion criteria

The inclusion criteria were being > 10 years of age, having been diagnosed with asthma, and having therefore been followed by a pulmonologist for at least three months. Pregnant women were excluded.

The following tools were used for the diagnosis of asthma: clinical assessment by a pulmonologist, spirometry, and chest X-ray. For diagnostic purposes, the physician considered reports of typical asthma symptoms, such as episodes of wheezing, coughing, or dyspnea lasting more than six months, and improvement of these symptoms with the use of a bronchodilator or inhaled corticosteroids. The physicians had access to the patients and to their medical records. Spirometry results were categorized as normal or indicative of obstructive lung disease. All patients underwent chest X-ray to exclude those with findings that were inconsistent with the diagnosis of asthma, as per the physician's discretion. HRCT was requested for all patients presenting with uncontrolled symptoms or spirometry findings consistent with obstructive lung disease despite the use of a high dose of inhaled medication (> 800 µg/day of budesonide or equivalent combined with a long-acting β_2 agonist). Patients in whom the HRCT findings were inconsistent with a diagnosis of asthma were excluded from the study.

Study procedure

All patients completed a questionnaire designed specifically for the study, the 6-item Asthma Control Questionnaire (ACQ-6),[9] and the questionnaire developed by Morisky et al.[10] Patients underwent spirometry, were asked about their educational background, and were evaluated in terms of their inhaler technique.

The first questionnaire, which was prepared specifically for the study by our research team, was designed to collect clinical and demographic data. The ACQ-6 questionnaire, which has been translated to Portuguese and validated for use in Brazil,[9] was used in order to measure the intensity of asthma symptoms. Lower scores on the ACQ-6 indicate fewer asthma symptoms. We used a cut-off point of 1.5 to distinguish between controlled and uncontrolled symptoms. The Morisky et al. questionnaire,[10] which was used in order to estimate treatment adherence, contains four questions that assess patient perceptions of their own treatment adherence. The total score ranges from 0 (good adherence) to 4 (poor adherence). Scores ≥ 2 were considered indicative of poor treatment adherence.

Patient inhaler technique was evaluated in terms of the number of errors made with the inhaler devices in use during the study period. Pulmonologists observed patients while they used the devices and classified them into two different groups, depending on whether or not there were any errors that affected the effectiveness of the inhaled medication. The results were recorded as the presence or absence of errors. The patients were also asked about their educational background, and the number of years of schooling was recorded. Kindergarten or preschool years were not counted. Patients with ≥ 10 years of schooling were classified as having a high level of education.

Patients underwent pulmonary function tests with a Koko spirometer (PDS Instrumentation Inc., Louisville, CO, USA). The recommendations of the American Thoracic Society for the test were followed. The spirometer software was updated with reference values for the Brazilian population. Those values were used in order to calculate FEV_1 and FVC, both as a percentage of the predicted value.

Statistical analysis

The primary objective of the study was to assess whether a low level of education is a risk factor for uncontrolled asthma. To that end, binary univariate and multivariate logistic regression analyses were conducted. In those analyses, level of education was inserted as a continuous variable (years of schooling), and asthma control was inserted as a dichotomous variable (controlled or uncontrolled asthma). Uncontrolled asthma was defined as an ACQ-6 score > 1.5, with or without spirometry findings indicative of obstructive lung disease. Obstructive lung disease was defined as a post-bronchodilator FEV_1/FVC ratio below the lower limit of normality and an FEV_1 < 80% of the predicted value.[11] We used the backward likelihood ratio method to input data into the model and the Hosmer-Lemeshow test to check the goodness of fit of the model. To identify collinearity, we used the tolerance test and calculated the variance inflation factor.

The secondary objective of the study was to assess whether patient level of education was associated with treatment adherence and correct inhaler technique. As in the previous analysis, level of education was assessed as a continuous variable. Treatment adherence and inhaler technique were assessed as dichotomous variables—good or poor adherence and presence or absence of errors, respectively. In addition, we compared the patients with ≥ 10 years of schooling and those with < 10 years of schooling in terms of the clinical and demographic characteristics. We used the Mann-Whitney test to compare continuous and ordinal variables, whereas we used the chi-square test to compare dichotomous variables. All analyses were conducted with the Statistical Package for the Social Sciences, version 13 (SPSS Inc., Chicago, IL, USA).

Ethical aspects

The study was approved by the Research Ethics Committee of the Jundiaí School of Medicine (Protocol No. 70427317.8.0000.5412). Written informed consent was obtained from the participating patients or from their parents or legal guardians.

RESULTS

Table 1 describes the clinical and demographic characteristics of the 358 patients included in the study. The majority of the patients were female. The median age was 49 years, and the median number of years of schooling was 7. The proportion of patients using moderate/high doses of inhaled medication (≥ 800 µg/day of budesonide or equivalent + a long-acting β_2 agonist) and of patients with uncontrolled asthma symptoms (ACQ-6 score > 1.5) was 55% and 32%, respectively. The spirometry findings were consistent with obstructive lung disease in 68 patients (19%). Table 1 also compares the characteristics of the patients, by level of education. In comparison with the patients with a higher level of education, those with a lower level of education were older, had a greater number of comorbidities, were more frequently exposed to rural environments, were more frequently vaccinated against influenza, and more often used moderate/high doses of inhaled asthma medications . The two groups were similar in terms of the ACQ-6 scores and the proportion of patients in whom the spirometry findings were consistent with obstructive lung disease. Treatment adherence was slightly better among the patients with a lower level of education, although the difference was not statistically significant. There was no difference between the two groups regarding the frequency of errors in inhaler use.

Table 2 shows the results of the binary logistic regression analysis adjusted for age, average monthly family income per household member, place of assessment (public or private outpatient clinic), and history of exposure to rural environments. The level of education, analyzed here as a continuous variable (years of schooling), was not found to be a risk factor for any of the indicators of severity: uncontrolled asthma symptoms, as determined by the ACQ-6 score (OR = 0.99, 95% CI: 0.94-1.05); spirometry findings consistent with obstructive lung disease (OR

Table 1. Characteristics of the study population and comparison by level of education.[a]

Characteristic	Sample as a whole (n = 358)	Years of schooling ≥ 10 (n = 126)	Years of schooling < 10 (n = 232)	p*
Female gender	227 (63)	85 (68)	142 (61)	0.19
Age, years	49 [19-63]	43 [33-55]	56 [15-66]	0.01
Monthly family income per household member, R$	1,066 [683-1,666]	1,312 [843-1,895]	950 [625-1,565]	< 0.01
Years of schooling	7 [4-11]	12 [11-14]	4 [3-7]	< 0.01
Body mass index, kg/m^2	27 [23-32]	27 [24-32]	26 [22-31]	0.02
Presence of comorbidities[b]	154 (43)	42 (34)	112 (48)	< 0.01
History of exposure to rural areas	193 (54)	46 (37)	147 (63)	< 0.01
Physical activity > 2 h/week	62 (17)	22 (18)	40 (17)	0.92
Former smoker	53 (15)	16 (13)	37 (16)	0.43
Rhinitis	258 (72)	97 (78)	161 (69)	0.09
Flu vaccination in the last year	241 (67)	69 (56)	172 (74)	< 0.01
Use of moderate/high doses of inhaled medication[c]	198 (55)	59 (47)	139 (60)	0.03
Previously intubated for asthma	14 (4)	5 (4)	9 (4)	0.58
Adequate environmental control	263 (74)	96 (77)	167 (72)	0.30
Device used for the administration of inhaled corticosteroids				
Spray	97 (27)	42 (34)	55 (24)	0.11
Capsule-based dry powder inhaler	225 (63)	73 (58)	152 (65)	
None	36 (10)	10 (8)	26 (11)	
Patients receiving inhaled corticosteroids for free[d]	228 (71)	81 (70)	147 (71)	0.91
Incorrect use of the inhaler[d]	34 (10)	16 (14)	18 (9)	0.15
ACQ-6 Score > 1.5	113 (32)	39 (30)	74 (32)	0.73
Good treatment adherence[d]	272 (85)	92 (80)	180 (88)	0.06
Post-bronchodilator FVC, % of predicted value	99 [87-110]	98 [88-107]	100 [86-112]	0.65
Post-bronchodilator FEV_1, % of predicted value	91 [75-105]	92 [77-104]	90 [74-106]	0.67
Spirometry findings consistent with obstructive lung disease	68 (19)	21 (17)	47 (20)	0.48

ACQ-6: 6-item Asthma Control Questionnaire. [a]Values expressed as n (%) or as median [interquartile range]. [b]At least one of the following: diabetes, systemic arterial hypertension, depression, and heart disease. [c]At least 800 µg/day of budesonide or equivalent + long-acting β_2 agonist. [d]Considering only the 322 patients using inhaled corticosteroids. *≥ 10 vs. < 10 years of schooling. Chi-square test for dichotomous variables; the Mann-Whitney test for ordinal and continuous variables.

Table 2. Binary logistic regression analysis of the association between the number of years of schooling and indicators of asthma severity.

Variables	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
ACQ-6 score > 1.5	1.02 (0.97-1.07)	0.99 (0.94-1.05)
Obstructive lung disease	0.96 (0.90-1.02)	1.00 (0.99-1.01)
Uncontrolled asthma[a]	0.97 (0.90-1.04)	1.03 (0.95-1.10)
Use of moderate/high doses of inhaled medication[c]	0.95 (0.90-0.99)	0.99 (0.94-1.06)

ACQ-6: Asthma Control Questionnaire with six questions. [a]ACQ-6 > 1.5 and/or obstructive lung disease on spirometry. [b]At least 800 µg/day of budesonide or equivalent + long-acting β_2 agonist.
*Adjusted for age, monthly family income per household member, place of assessment (public or private clinic), and history of rural exposure.

= 1.00; 95% CI: 0.99-1.01); use of moderate/high doses of inhaled medication (OR = 0.99; 95% CI: 0.94-1.06); and uncontrolled asthma (OR = 1.03, 95% CI: 0.95-1.10).

Figures 1 and 2 show the number of years of schooling, in medians and interquartile ranges (IQRs), in relation to treatment adherence and inhaler technique, respectively. The level of education (number of years of schooling) was similar between the group of patients in whom treatment adherence was good and that of those in whom it was poor—7 years (IQR: 4-11) vs. 8 years (IQR: 4-12, p = 0.08)—as well as between the group of patients who made errors in the use of their inhaler and that of those who did not—8 years (IQR: 4-12) vs. 7 years (IQR: 4-11, p = 0.41).

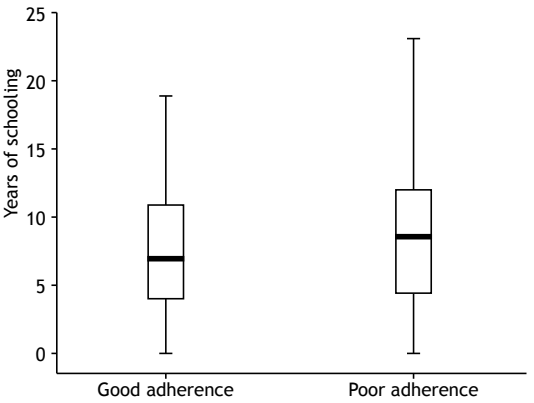

Figure 1. Number of years of schooling, by level of treatment adherence. p = 0.08 between the two groups.

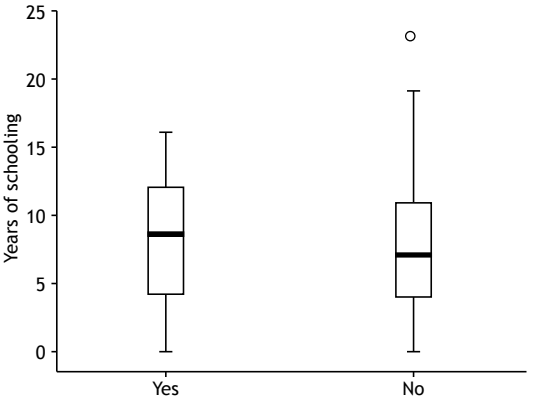

Figure 2. Number of years of schooling, by quality of inhaler technique. p = 0.41 between the two groups.

DISCUSSION

Our results suggest that a low level of education is not a risk factor for uncontrolled asthma. In our sample, patients had access to pulmonologists and to treatment. Previous studies have shown that individuals in situations of social vulnerability (with a low level of education and a low income) are at greater risk of uncontrolled asthma.[2-4,12] However, in those studies,[2-4,12] the patients had no guaranteed access to a physician or to treatment. Our study adds new information to the literature, indicating that it is possible to control asthma in individuals with a low level of education if access to a specialist physician and to treatment is facilitated. In recent years, several initiatives have been implemented with the aim of expanding patient access to asthma treatment. The results have been promising, at the local level.[5,7] Nevertheless, because the proportion of individuals with uncontrolled asthma is still quite high in the general population,[8] these initiatives need to be further expanded.

The literature indicates that patients with fewer years of schooling have more difficulty adhering to therapy and making proper use of inhalers.[1] Our study did not produce similar results. The good levels of treatment adherence currently seen in Brazil are probably due to easier access to medication, which is dispensed for free.[5,7] The high rate of patients who use inhalers correctly can probably be attributed to increased physician awareness of the need to train patients in their use. In addition, there are new devices that are simpler to use and, therefore, less subject to errors. Most of the patients in our study sample were using capsule-based dry powder inhalers, which are easier to use. These factors probably contributed to the fact that the level of education was not found to be a limiting factor for asthma control.

One limitation of the present study was the fact that our patients were being followed by a specialist physician (a pulmonologist). Therefore, the results cannot be generalized to patients who are being followed by general practitioners. Another potential limitation is that, in our sample, patients with a lower level of education had more often been exposed to rural environments, which could potentially modify asthma.[13-15] We attempted to minimize this confounder by adjusting the binary logistic regression analysis for

a history of such exposure. Age is another factor that modifies the severity of asthma.[16,17] In our sample, the patients with a lower level of education were older than were those with a higher level of education. Therefore, the analyses that assessed the relationship between level of education and asthma control were adjusted for patient age. Our study also has several strengths, including the fact that we evaluated patients seen at public and private clinics, as well as patients in various age groups. That increases the external validity of our results. Another noteworthy aspect is that we used validated instruments to quantify asthma control and treatment adherence.

In conclusion, a low level of education does not appear to be a risk factor for inadequate asthma control in a population of patients with access to specialist physicians and to treatment. In addition, patient level of education is apparently not a limiting factor for adequate treatment adherence or proper inhaler technique. Therefore, a low level of education does not seem to be the cause of the high morbidity of asthma in populations in situations of social or economic vulnerability. It is likely that asthma control in these populations depends mainly on facilitating access to medical specialists and to treatment.

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Obstructive sleep apnea and quality of life in elderly patients with a pacemaker

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ABSTRACT

Objective: To evaluate quality of life in elderly patients with obstructive sleep apnea (OSA) who have a pacemaker. **Methods:** This was a cross-sectional study involving elderly patients (≥ 60 years of age) with a pacemaker. The dependent variable was quality of life, as evaluated with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). Sociodemographic and clinical parameters, including anxiety and depression (Hospital Anxiety and Depression Scale score), as well as the presence of OSA (defined as an apnea-hypopnea index ≥ 15 events/h), were analyzed as independent variables. Patients with cognitive/neurological deficits or decompensated heart failure were excluded. **Results:** We evaluated 72 patients, 17 (23.6%) of whom presented OSA. Of those 17 patients, 9 (52.9%) were male. The mean age was 72.3 ± 9.3 years. A diagnosis of OSA was not associated with gender (p = 0.132), age (p = 0.294), or body mass index (p = 0.790). There were no differences between the patients with OSA and those without, in terms of the SF-36 domain scores. Fourteen patients (19.4%) presented moderate or severe anxiety. Of those 14 patients, only 3 (21.4%) had OSA (p = 0.89 vs. no OSA). Twelve patients (16.6%) had moderate or severe depression. Of those 12 patients, only 2 (16.6%) had OSA (p = 0.73 vs. no OSA). **Conclusions:** In elderly patients with a pacemaker, OSA was not found to be associated with quality of life or with symptoms of anxiety or depression.

Keywords: Quality of life; Aged; Sleep apnea, obstructive.

INTRODUCTION

Obstructive sleep apnea (OSA) is a respiratory disorder that is quite common, affecting up to one third of the adult population and reaching an even higher prevalence in the elderly.[1] It has been associated with various adverse events, including cardiovascular disease, occupational problems, and motor vehicle accidents, resulting in decreased quality of life (QoL), as well as increased morbidity and mortality.[2-4]

It is understood that QoL is something intrinsic that can be evaluated only by the individual in question. Because expectations regarding health and the ability to deal with limitations can affect the self-perception of health and satisfaction with life, two individuals with the same health status may evaluate their QoL in very different manners.[5-7]

In recent decades, there has been a clear demographic change in Brazil, in terms of the aging of the population, which has followed the pattern observed in many other developing countries. It is estimated that, by 2020, the elderly population in Brazil will be the sixth largest in the world, comprising approximately 32 million people.[8,9]

The classic signs and symptoms of illness are not direct correlates of the psychic and social aspects of life in elderly individuals, because well-being in old age requires a balance among the various dimensions of QoL. The concept of QoL in old age is more closely related to autonomy and independence than to the presence or absence of disease.[6,10] Therefore, self-assessment is not only quite practical but is also strongly associated with the actual health status in the elderly.[6,10,11]

OSA can affect important QoL domains, such as limitations in activities of daily living, emotional aspects, and interpersonal relationships, none of which are explored during a sleep study. Therefore, the objective of the present study was to evaluate QoL, as well as to determine whether OSA is associated with QoL, in elderly individuals.

METHODS

This was a cross-sectional cohort study. The study population was composed of 72 elderly patients (≥ 60 years of age), all of whom had a pacemaker, treated between December of 2013 and September of 2014 at the Outpatient Pacemaker Clinic of the *Pronto-Socorro Cardiológico Universitário de Pernambuco* (PROCAPE University of Pernambuco Emergency Cardiology Hospital), located in the city of Recife, Brazil. The dependent variable was QoL. The following were analyzed as independent variables: age, gender, level of education, level of physical activity, anxiety, depression, use of psychotropic medications, presence of OSA, excessive daytime sleepiness, body mass index, systemic arterial hypertension, acute myocardial infarction, and diabetes

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mellitus. Patients with cognitive or neurological deficits were excluded, as were those with decompensated heart failure. The research protocol was developed in accordance with Brazilian National Health Council Resolution no. 466/2012, which deals with the ethical aspects of research involving human beings in Brazil. After permission to carry out the study at the PROCAPE Outpatient Pacemaker Clinic had been obtained, the project was submitted to the Research Ethics Committee of the Hospital Oswaldo Cruz/PROCAPE, via the *Plataforma Brasil* (CAAE no. 07859513.4.0000.5207). All participating patients gave written informed consent.

Instruments for assessment

All data were collected by the same researcher. Demographic and clinical data were obtained from an interview with the patient, in which standardized data collection forms were used.

Medical Outcomes Study 36-item Short-Form Health Survey

The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) is a generic, self-report questionnaire consisting of 36 items grouped into eight domains[12]: functional capacity, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Higher SF-36 scores indicate better QoL.

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) comprises fourteen items, divided into two subscales with seven items each[13]: the anxiety subscale; and the depression subscale. Each item is scored from 0 to 3, the maximum score therefore being 21 for each of the subscales. To avoid any influence of somatic disturbances on the scores, we excluded all questions regarding symptoms of anxiety or depression that were related to physical disorders (e.g., dizziness, headaches, insomnia, and fatigue). Questions regarding symptoms related to severe mental disorders were also excluded, given that the HADS has been shown to be a valid, reliable instrument for evaluating anxiety or depression in nonpsychiatric patients.[14]

Sleep study

All participants underwent overnight monitoring in the PROCAPE Sleep and Heart Laboratory, with a portable respiratory monitor (Embletta, PDS; Medcare, Reykjavik, Iceland). The monitoring involved continuous oximetry, the use of a thoracoabdominal belt for detecting respiratory work, monitoring of airflow through a nasal cannula, the use of position sensors, heart rate recording (through pulse oximetry), and snore detection. Apnea was defined as a > 90% reduction in airflow, whereas hypopnea was defined as a 30% reduction in airflow, accompanied by a 4% decrease in oxygen saturation.[14] The final result was expressed in terms of the apnea-hypopnea index, calculated by dividing the total number of apnea and hypopnea events by the total sleep time, in hours. An apnea-hypopnea index ≥ 15 events/h was considered diagnostic of OSA. In addition, daytime sleepiness was assessed subjectively with the Epworth Sleepiness Scale.[15] A total score > 10 was considered indicative of excessive daytime sleepiness.[16]

Statistical analysis

In the data analysis, categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as means and standard deviations or as medians and interquartile ranges. Comparisons of proportions between two or more groups were performed with Pearson's chi-square test. For the comparison of means, we used the Student's t-test for independent samples, whereas we used the Mann-Whitney test for the comparison of medians. In all tests, the level of significance adopted was $p < 0.05$. Statistical analyses were performed with the Stata software, version 12.1SE (StataCorp LP, College Station, TX, USA).

RESULTS

Of the 72 patients evaluated, 17 (23.6%) had OSA. Of those 17 patients, 9 (52.9%) were male. The mean age was 73.4 years among the patients with OSA and 70.8 years among those without. Other demographic and clinical characteristics of the patients with and without OSA are shown in Table 1.

For the sample as a whole, the mean score on the Physical Component Summary of the SF-36, which encompasses the physical domains (functional capacity, role-physical, bodily pain, and general health), was 56.6. Among those domains, the mean score was lowest (49.0 ± 25.6) for the role-physical domain and highest (60.8 ± 28.3) for the bodily pain domain. On the Mental Component Summary of the SF-36, which encompasses the vitality, social functioning, role-emotional, and mental health domains, the mean score was 69.2, being lowest (67.6 ± 26.8) for the mental health domain and highest (70.5 ± 29.9) for the social functioning domain.

There were no significant differences between the patients with and without OSA when the SF-36 domains were assessed separately. However, for five domains (functional capacity, role-physical, vitality, role-emotional, and mental health), the patients with OSA had higher (i.e., better) scores. Among the patients with OSA, the mean score was lowest (50.0 ± 29.3) for the role-physical domain and highest (75.6 ± 17.1) for the vitality domain. Comparing the mean scores obtained for each domain of the SF-36 (Table 2), we found that the scores were highest for the domains within the Mental Component Summary (vitality, social functioning, role-emotional, and mental health).

On the anxiety subscale of the HADS, 40 patients (55.6%) presented scores within the normal range; 18 (25.0%) presented scores indicative of mild anxiety; and only 14 (19.4%) presented scores indicative of

Table 1. Demographic and clinical characteristics of patients with pacemakers, with and without obstructive sleep apnea.[a]

Characteristic	Group		p*
	Without OSA (n = 55)	With OSA (n = 17)	
Male gender	18 (32.7)	9 (52.9)	0.132
Age, years	70.8 ± 8.7	73.4 ± 9.3	0.294
BMI, kg/m^2	27.4 ± 4.6	27.7 ± 5.0	0.790
Underweight	7 (13.0)	2 (11.8)	0.991
Normal weight	19 (35.2)	6 (35.3)	
Overweight	28 (51.9)	9 (52.9)	
Level of education			0.948
Illiterate	14 (25.5)	5 (29.4)	
Literate	27 (49.1)	8 (47.2)	
≥ 9 years of schooling	14 (25.5)	4 (23.5)	
Physically active	12 (21.8)	3 (17.6)	0.711
Anxiety			0.888
None	31 (56.4)	9 (52.9)	
Mild	13 (23.6)	5 (29.4)	
Moderate to severe	11 (20.0)	3 (17.6	
Depression			0.726
None	41 (74.5)	13 (76.5)	
Mild	4 (7.3)	2 (11.8)	
Moderate to severe	10 (18.2)	2 (11.8)	
Use of psychoactive medications	8 (14.5)	3 (17.6)	0.756
Excessive daytime sleepiness			0.947
None	17 (30.9)	5 (29.4)	
Moderate risk	5 (9.1)	2 (11.8)	
High risk	33 (60.0)	10 (58.8)	
AHI, events/h	7.4 [4.5-12.0]	26.9 [23.2-35.7]	<0.001
Minimum SpO_2, %	87 [79-90]	82 [72-84]	0.006
Oxygen desaturation index, events/h	7.4 [3.2-12.6]	29.0 [18.0-34.9]	0.000
Time at SpO_2 < 90%, h	0.5 [0-2.1]	2.8 [1.4-9.9]	0.002
Comorbidities			
Acute myocardial infarction	10 (18.5)	4 (23.5)	0.651
Systemic arterial hypertension	42 (77.8)	13 (76.5)	0.910
Diabetes mellitus	14 (25.9)	1 (5.9)	0.077
Dyslipidemia	18 (34.0)	6 (33.3)	0.961

OSA: obstructive sleep apnea; BMI: body mass index; and AHI: apnea-hypopnea index. [a]Values expressed as n (%), mean ± SD, or median [interquartile range]. *Proportions compared by Pearson's chi-square test; means compared by Student's t-test; and medians compared by the Mann-Whitney test.

Table 2. Mean scores on the Medical Outcomes Study 36-item Short-Form Health Survey, by domain, among patients with pacemakers: comparison between patients with and without obstructive sleep apnea.[a]

Domain	Group		p*
	With OSA (n = 55)	Without OSA (n = 17)	
Functional capacity	57,3 ± 25,9	67,1 ± 24,2	0,171
Role-physical	48,6 ± 30,6	50,0 ± 29,3	0,872
Bodily pain	61,4 ± 27,6	59,2 ± 31,4	0,783
General health	57,4 ± 19,5	56,4 ± 20,7	0,847
Vitality	66,6 ± 24,4	75,6 ± 17,1	0,164
Social functioning	71,1 ± 29,8	68,4 ± 31,0	0,743
Role-emotional	69,1 ± 30,0	72,5 ± 31,7	0,683
Mental health	66,6 ± 27,5	70,8 ± 25,1	0,576

OSA: obstructive sleep apnea. [a]Values expressed as mean ± SD. *Student's t-test for independent samples.

moderate or severe anxiety. Of those 14 patients, only 3 (21.4%) had OSA. As can be seen in Figure 1, the score on the HADS anxiety subscale was not found to be associated with a diagnosis of OSA (p = 0.89).

On the depression subscale of the HADS, 54 patients (75.0%) presented scores within the normal range; 6 (8.3%) presented scores indicative of mild depression; and 12 (16.6%) presented scores indicative of moderate or severe depression. Of those 12 patients, only 2 (16.6%) had OSA. As can be seen in Figure 2, the score on the HADS depression subscale was not found to be associated with a diagnosis of OSA (p = 0.73).

DISCUSSION

The present study evaluated QoL in elderly patients with and without OSA, producing some interesting data. The comparison of the means of the variables related to SF-36 domains between the patients with and without OSA did not reveal any associations between QoL and the presence of OSA. None of the SF-36 domains were found to be associated with OSA.

Because our study population consisted exclusively of elderly individuals, certain specific characteristics of that population could explain the results obtained. With advancing age, most physiological functions deteriorate, which contributes to sleep fragmentation in the elderly. Therefore, the prevalence of sleep-disordered breathing is expected to increase with age, as is that of OSA.[17] However, in our study sample, the prevalence of OSA was relatively low (≈ 24%) in comparison with the 37-44% reported in other population-based studies with subgroups of the same age.[1,18] That finding might be attributable to the lower mean body mass index in our sample (≈ 27 kg/m^2) and the use of portable monitoring with a more rigorous oxygen desaturation criterion (4% difference), without the use of electrocardiography.[18] However, that does not imply that OSA necessarily has a negative impact on QoL. It should be born in mind that the instrument used for the evaluation of QoL, the SF-36, evaluates subject perceptions; that is, it involves a subjective evaluation that is influenced by several factors. Therefore, even when all of the limitations imposed by age are present, elderly individuals can perceive that scenario in a variety of ways. One of the factors associated with good health in the elderly is social engagement in activities of daily living, and this aspect is not contemplated in scales that assess QoL or in scales designed to quantify anxiety and depression.

In a study using the SF-36 to analyze the impact that the symptoms of OSA, especially excessive daytime sleepiness, have on QoL in individuals over 65 years of age (n = 103), in comparison with younger subjects (n = 109), Martínez-García et al.[19] also found no significant association between the presence of OSA and impaired QoL in the elderly. The authors emphasized the fact that, according to many studies, the elderly attribute excessive daytime sleepiness to their age, to the use of certain medications, or to a reduction in physical capacity, rather than to a pathological condition.[19]

It is known that the elderly are affected by some serious mental disorders, mainly those related to verbal activity, attention, memory, and logical reflection.[20] The cognitive deficit often observed in the elderly might also have contributed to a distorted assessment of QoL in the present study. A cognitive deficit could itself be associated with OSA.[21-23]

Another aspect that could explain the results obtained in the present study is the profile of the population studied. Our sample predominantly comprised individuals in a social situation characterized by many restrictions, their lower socioeconomic status obliging them to use public health care services. That population is not given sufficient attention or sufficient time to talk about their life and their overall health status during medical consultations. Many of our patients reported that during the application of the questionnaires they felt heard and accepted. That feeling could have contributed to the negative symptoms being underestimated, as a reflection of their QoL.

In a study involving a total of 63 subjects, Glebocka et al.[20] evaluated the relationship between OSA, QoL, and psychological performance. The authors concluded that there were no significant differences between the subjects with and without OSA, in terms of the

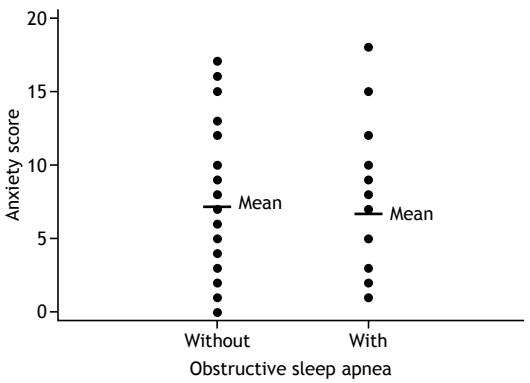

Figure 1. Distribution of scores on the anxiety subscale of the Hospital Anxiety and Depression Scale among patients with pacemakers, with and without obstructive sleep apnea.

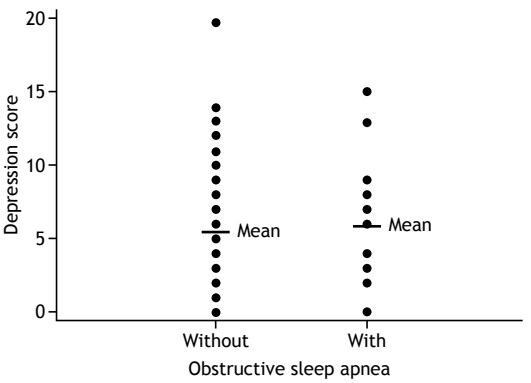

Figure 2. Distribution of scores on the depression subscale of the Hospital Anxiety and Depression Scale among patients with pacemakers, with and without obstructive sleep apnea.

positive or negative emotions experienced. One possible explanation for the absence of psychiatric disorders in patients with OSA is that such patients might experience an improvement in their mood after admission to the hospital, in anticipation of being cared for by health care professionals and being given a diagnosis.

All of the domains studied by Dutt et al.[4] and Lacasse et al.[24] were affected by OSA, suggesting that QoL is impaired in patients with OSA, a finding corroborated by Iacono Isidoro et al.,[25] who pointed out that even mild OSA has a negative impact on QoL. However, in all of those studies,[4,24,25] the individuals evaluated were < 60 years of age. Other studies have also indicated that OSA results in impaired QoL,[26-30] although few of those studies involved elderly patients. Even in the few studies that included elderly individuals, differences in relation to the mean age of the study population should be considered. For example, Baldwin et al.[31] found that sleep-disordered breathing had a negative impact on all SF-36 domains in a population of elderly individuals with a mean age of 63.2 years. That differs from the mean age of our study sample (72.1 years), which is comparable to that of the sample studied by Martínez-García et al.,[19] who pointed out that many authors have proposed the existence of two types of OSA, depending on the age of the affected individual. The type of OSA that occurs in younger individuals has a more evident symptomatology, whereas the type that occurs in older individuals has a more uncertain impact. The factors associated with sleep quality differ between younger and older individuals. Those differences reflect an age-related progression, which is universal, rather than a specifically cultural phenomenon.[30]

Another notable aspect is the potential influence that confounding factors, such as lifestyle, chronic diseases, and the regular use of psychotropic medications, have on the association between QoL and OSA.[19] In the elderly, there are underdiagnosed diseases that alter QoL and affect sleep quality.

The sample of patients evaluated in the present study had some characteristics that could limit the external validity of our results: each of the elderly patients evaluated had a pacemaker, and a significant proportion were illiterate or had a very low level of education. Although the study design does not allow for conclusions about a cause-and-effect relationship, we highlight the inclusion of a comparison group of elderly individuals with pacemakers and OSA.

The results of the present study suggest that OSA is not associated with QoL in elderly patients with pacemakers.

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ORIGINAL ARTICLE

Back to the future: a case series of minimally invasive repair of pectus excavatum with regular instruments

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ABSTRACT

Objective: Minimally invasive repair of pectus excavatum (MIRPE) is a surgical treatment for PE. During the procedure, a specialized introducer is used to tunnel across the mediastinum for thoracoscopic insertion of a metal bar. There have been reported cases of cardiac perforation during this risky step. The large introducer can be a dangerous lever in unskilled hands. We set out to determine the safety and feasibility of using regular instruments (i.e., not relying on special devices or tools) to create the retrosternal tunnel during MIRPE. **Methods:** This was a preliminary study of MIRPE with regular instruments (MIRPERI), involving 28 patients with PE. We recorded basic patient demographics, chest measurements, and surgical details, as well as intraoperative and postoperative complications. **Results:** Patients undergoing MIRPERI had Haller index values ranging from 2.58 to 5.56. No intraoperative complications occurred. Postoperative complications included nausea/vomiting in 8 patients, pruritus in 2, and dizziness in 2, as well as atelectasis, pneumothorax with thoracic drainage, pleural effusion, and dyspnea in 1 patient each. **Conclusions:** In this preliminary study, the rate of complications associated with MIRPERI was comparable to that reported in the literature for MIRPE. The MIRPERI approach has the potential to improve the safety of PE repair, particularly for surgeons that do not have access to certain special instruments or have not been trained in their use.

Keywords: Funnel chest; Heart injuries; Thoracic wall; Intraoperative complications; Minimally invasive surgical procedures.

INTRODUCTION

Minimally invasive repair of pectus excavatum (MIRPE) was first performed in 1987 and was presented to the American Pediatric Surgical Association in 1997. In the procedure, specialized MIRPE tools are used in order to create a retrosternal tunnel for the placement of one or more metal bars to elevate the sternum. The metal bars remain in the chest until their removal several years later.[1] This technique quickly gained popularity as an alternative to the conventional open repair technique, and the number of patients presenting for surgical correction of PE has increased exponentially. Although it is not without complications, MIRPE is currently considered the standard of care for the management of PE.[2]

Although bar displacement, infection, and pneumothorax are the most common complications of MIRPE, life-threatening complications have also been reported.[3,4] The riskiest step of the procedure, accounting for these severe complications, is the dissection of the mediastinum to create the tunnel. This step has been linked to many cases of cardiac injury requiring urgent thoracotomy or even resulting in death.[5,6]

To improve safety during mediastinal dissection, several technical modifications have been proposed. For instance, thoracoscopy is reportedly used in the majority (83.7%) of cases.[7] However, even with thoracoscopy-guided retrosternal tunnel dissection, cases of cardiac perforation and pericardial laceration have been described. Therefore, the potential for cardiac injury remains despite direct visualization of the pericardium.[8,9] A recently published systematic review of the literature on life-threatening complications of MIRPE showed that there have been 12 published cases and 15 unreported cases of cardiac injuries, resulting in 9 deaths.[10] Those numbers likely represent an underestimation.

Mediastinal dissection is dangerous primarily because of two incompatible aspects. The pectus introducer—a dedicated tool developed to create the tunnel—is a very long (58.6 cm) instrument that can become a dangerous lever in unskilled hands. At the same time, the retrosternal region, ordinarily a narrow anatomical space, is further narrowed in individuals with PE, because of the dorsal deviation of the sternum. Given this difficulty, the aim of the present study was to evaluate retrosternal tunnel dissection in a case series of patients undergoing MIRPE without the use of the pectus introducer. Instead, we opted for the exclusive use of a regular surgical instrument, a Crawford clamp. We refer to this technique as MIRPE with regular instruments (MIRPERI).

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METHODS

Between March of 2014 and August of 2016, 31 patients with PE were included in a prospective case series designed to evaluate the safety and effectiveness of MIRPERI. The study was conducted in the Thoracic Surgery Department of the Heart Institute of the University of São Paulo School of Medicine *Hospital das Clínicas*. The study was approved by the Research Ethics Committee of the *Hospital das Clínicas* (Registration no. UIN 2545), and all participating patients gave written informed consent.

The inclusion criteria followed those applied in our MIRPE practice, to include patients from 11 years old. Although we do not encourage the use of MIRPE in mature patients, we have no specific upper age limit, because it is an intraoperative decision: if the chest wall is too rigid, we convert to a combined (MIRPE and Ravitch) technique. Patients showing a complex (carinatum/excavatum) morphology were excluded, as were those with skeletal diseases, coagulation dysfunction, cutaneous diseases affecting the chest wall, or angiopathies, as well as those who were pregnant or obese, obesity being defined as a body mass index > 30 kg/m^2.

The standardized evaluation carried out for patient selection was the same as that routinely used at our facility to identify candidates for surgical treatment of PE. It involves clinical history taking, physical examination, and laboratory tests (including pulmonary function tests), chest X-rays, cardiac evaluation (electrocardiography and echocardiography), and a baseline low-dose computed tomography (CT) scan of the chest. Before the CT scans were acquired, patients were instructed to breathe normally. Low-dose CT scans were then performed with the patients in respiratory pause during quiet inspiration. From the CT scans acquired at the deepest point of the deformity, the following measurements were taken (Figure 1): the sagittal distance between the posterior aspect of the sternum and the anterior spine; the side-to-side distance; the sagittal distance of the right and left hemithoraces; the sternal rotation angle; and the sagittal distance between the posterior sternum in its hypothetical corrected position and the anterior spine, minus the distance between the posterior sternum in its actual position and the anterior spine. On the basis of those data, it was possible to calculate the Haller index, correction index, sternal rotation angle (< 30° vs. ≥ 30°), and chest wall asymmetry index.[11-13]

We have previously described in detail the MIRPE technique that we usually employ.[14,15] To highlight the modifications that we propose, the main steps of the procedure are summarized. The patients are intubated with single-lumen tracheal tubes. The use of ventilation at lower volumes or with shorter periods of apnea precludes the need for double-lumen intubation. The skin is marked at the point of deepest depression on the midline and at the hinge point in each hemithorax. An incision is made laterally to the hinge points in each

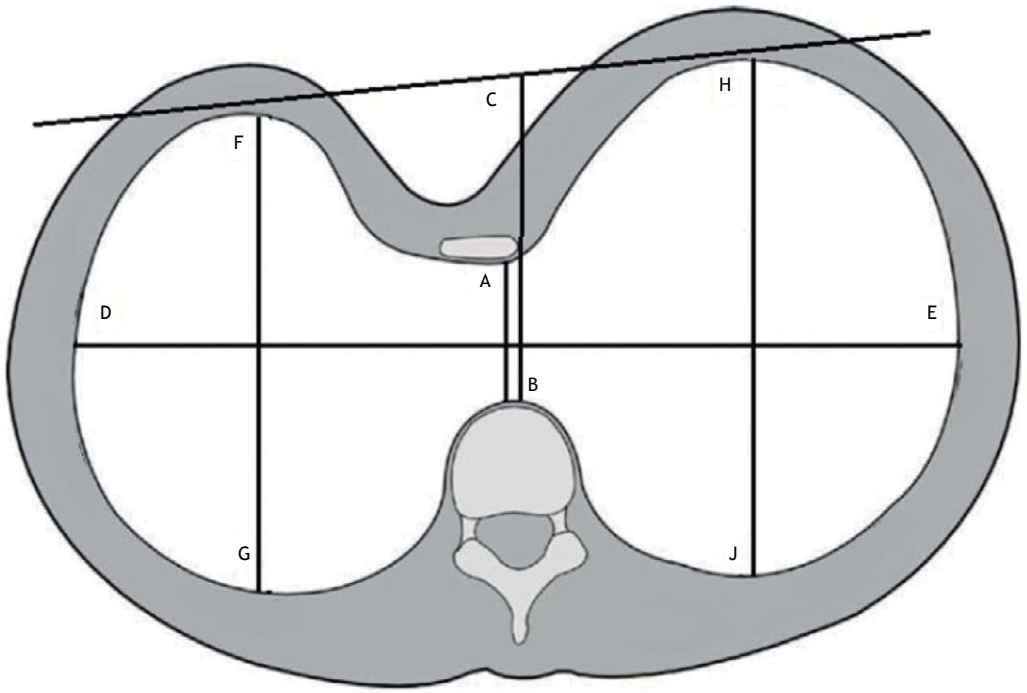

Figure 1. Thoracic schematic diagram of the thorax, with measurements: the sagittal distance between the posterior aspect of the sternum (A) and the anterior spine (B); the sagittal distance between the posterior sternum (C) in its hypothetical corrected position and the anterior spine (B), minus the distance between the posterior sternum in its actual position and the anterior spine (B); the side-to-side distance (D–E); the sagittal depth of the right and left hemithoraces (F–G and H–J); and the sternal rotation angle (F–C–H).

hemithorax, and a subcutaneous tunnel is created in the direction of the hinge points.

Although some surgeons prefer a right-to-left approach, we first enter the left thoracic cavity with the camera at the hinge point. Though the same incision, a 5.5-mm blunt trocar is introduced into the intercostal space immediately below the hinge point, and the camera is transferred to this lower space. A 24-cm long Crawford clamp is introduced at the hinge point, and, while the thoracoscope and the clamp are displacing the pericardium downward, the retrosternal tunnel is dissected with gentle movements (Figures 2 and 3).

As soon as the mediastinal midline is crossed, the thoracoscope is introduced on the right side and another Crawford clamp is used in order to displace the fat pad, thus avoiding injury to the major arteries that connect the internal mammary vessels and the anterior superior phrenic vessels that are found in 12.5% of right thoracic cavities and in 44.0% of left thoracic cavities.[16]

When the Crawford clamp crosses the fat pad and reaches the right hemithorax, a 28 F chest tube is placed through the hinge point incision inside the right hemithorax and it is brought back to the left hemithorax. The chest tube in the retrosternal tunnel represents a safe path to guide the pectus introducer or even the metal bar (Figure 4). The remainder of the surgery proceeds as usual.

To evaluate the safety and effectiveness of the MIRPERI technique, we recorded basic patient demographics, chest measurements, and surgical details. We also evaluated intraoperative and postoperative complications.

RESULTS

The basic characteristics of all 31 patients evaluated for inclusion in this case series are summarized in Table 1. In three cases (patients 3, 4, and 7), the defect was severe or the chest wall was too rigid. In those cases, we decided to use chondral cartilage resection through a midline incision before the metal bar was inserted under the sternum (combined MIRPE + Ravitch technique). The retrosternal tunnel was made with a combined bilateral approach, and those three cases were excluded from our analyses. Figure 5 demonstrates one such case.

Of the 28 patients that underwent MIRPERI and were included in the analysis, 6 (21.4%) were female. In this patient sample, the mean age was 16 ± 3 years (range, 11-26 years) and the mean body mass index was 18.2 ± 2.3 kg/m^2 (range, 14.0-22.3 kg/m^2). The mean Haller index was 3.73 ± 0.87 (range, 2.58-5.56) and was similar between males and females (3.80 ± 0.90 and 3.47 ± 0.71, respectively). Of the 28 patients, 22 (78.5%) received one bar and 6 (21.4%) received two bars. The mean duration of anesthesia was 220 ± 38 min (range, 150-305 min). No intraoperative complications occurred.

In one case, a chest tube was used because of pneumothorax in the postoperative period. One patient developed pleural effusion that was detected by chest X-ray, although the effusion was minimal and resolved spontaneously. The other postoperative complications were nausea/vomiting in 8 patients, pruritus in 2, dizziness in 2, atelectasis in 1, and dyspnea in 1. No surgical site infections were observed. No other severe complications occurred. The mean hospital stay was 5 ± 1 days (range, 3-7 days).

DISCUSSION

In this study, we evaluated the safety and feasibility of MIRPERI, a slightly modified version of the MIRPE in which regular instruments are used for retrosternal tunnel dissection. In our sample of 28 patients, the complication rates were comparable to those reported in the literature for MIRPE,[4] and there were no severe intraoperative or postoperative complications.

The proposal to use regular instruments to create a retrosternal tunnel for the correction of PE might sound like a throwback to some. In the early years of PE correction, the Nuss procedure was performed with regular surgical instrumental, although at that time the approach to dissection of the tunnel was from the right side and did not involve video assistance. The subsequent evolution of the technique was based on the development of dedicated instruments and the more recent development of tools that are even more specific. Therefore, it is understandable that the use of regular instruments would be considered regressive. However, that is not the case, as will be discussed below.

Although it is unquestionable that MIRPE with the Nuss procedure represented a major advancement in the surgical treatment of PE, it is also worrisome that the safety of the procedure is still debated, as well as that the real incidence of major and life-threatening complications remains unknown.[10,17] The creation of the retrosternal tunnel, the most feared moment in the procedure, due to the risk of cardiac injury, continues to be the source of major complications. In addition to the technical difficulty of handling the large pectus introducer within the narrow mediastinal space, there are two other aspects that can complicate this step, one anatomic and the other epidemiological. From an anatomic standpoint, the heart is usually dislodged to the left in PE, making the retrosternal tunnel dissection from the right to the left hemithorax seem illogical. From an epidemiological standpoint, except at centers with a large number of cases of PE, MIRPE is not a common procedure. As a result, a general thoracic or pediatric surgeon may not have had many opportunities to become skilled at using the pectus introducer.

Many surgeons have proposed technical modifications to reduce the risk of cardiac injury in MIRPE. These include using a subxiphoid incision to allow finger guidance to the mediastinal dissection[18,19] and beginning the mediastinal dissection with the introducer

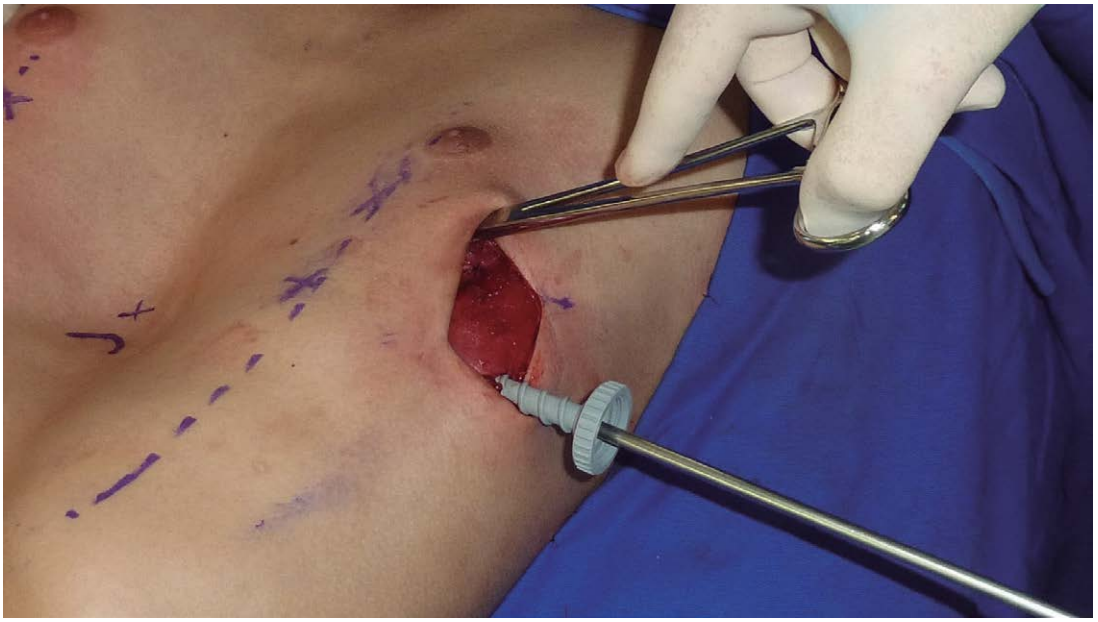

Figure 2. Tunnel dissection with regular instruments from the left side.

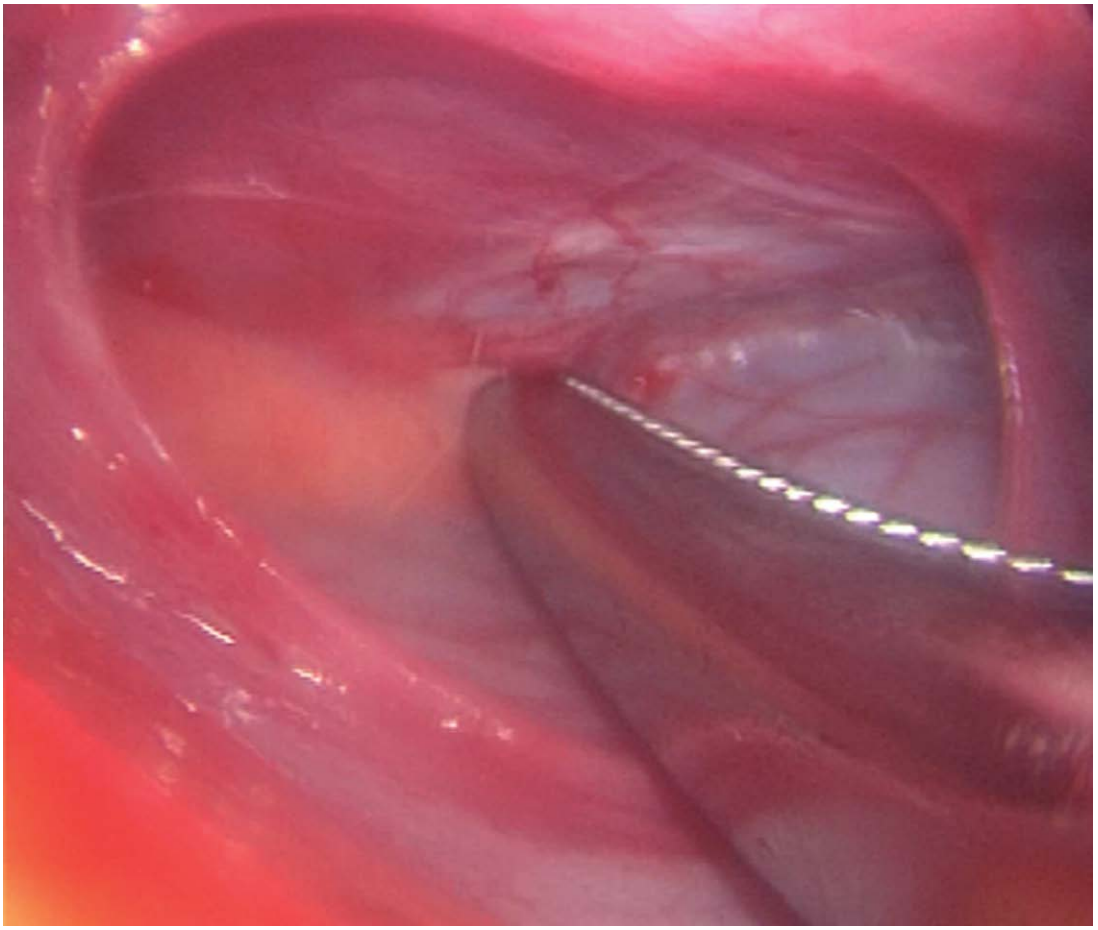

Figure 3. Thoracoscopic view of retrosternal tunnel dissection from the left hemithorax.

in a more cranial position and gradually proceeding distally.[20] However, the use of those techniques results in additional scars on the anterior chest wall that can be considered unacceptable, given that most PE patients elect to undergo this type of surgical procedure for cosmetic improvement. Another group

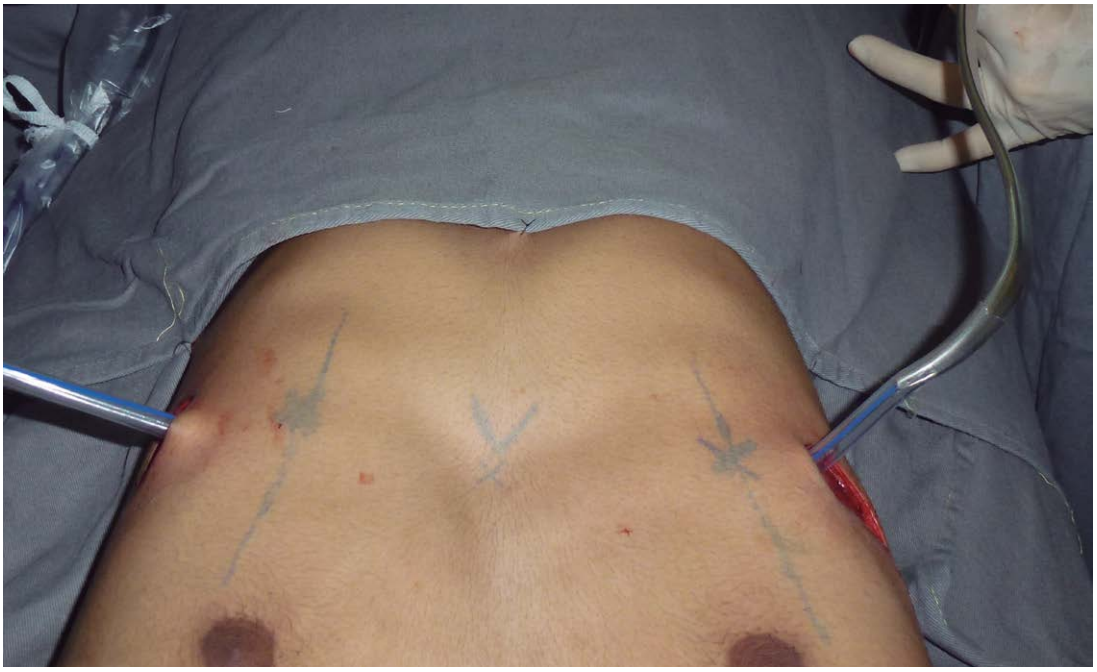

Figure 4. Chest tube passed through the retrosternal tunnel.

Table 1. Basic patient information, including gender, age, body mass index, Haller index, correction index, sternal rotation angle, number of metal bars utilized in the procedure, and length of the hospital stay.

ID	Gender	Age (years)	Body mass index (kg/m²)	Haller index	Correction index	Sternal rotation (°)	Bars (n)	Hospital stay (days)
1	M	15	15.12	3.11	25.00	26	2	5
2	M	20	20.20	2.58	20.75	13	1	6
3*	M	23	19.62	6.16	61.51	24	2	6
4*	F	14	11.15	30.38	90.18	19	1	8
5	M	14	17.01	4.19	38.71	0	1	6
6	M	17	19.97	4.52	43.14	26	2	3
7*	M	28	20.65	2.97	35.23	25	1	5
8	M	11	15.74	2.91	33.13	28	1	6
9	M	15	17.10	5.53	52.46	30	2	5
10	F	13	15.05	3.50	32.95	36	1	6
11	M	17	22.09	5.56	48.50	0	2	5
12	M	20	21.97	4.57	38.05	0	1	5
13	F	14	18.78	3.05	26.51	15	1	3
14	M	20	17.53	2.73	20.85	13	1	6
15	M	13	14.84	4.91	30.76	19	1	5
16	F	16	19.36	2.62	23.80	22	1	5
17	M	18	19.59	4.71	32.46	0	1	7
18	M	16	19.60	3.68	32.66	30	1	5
19	M	15	18.08	4.65	46.88	30	1	5
20	M	16	20.20	2.58	26.80	0	1	5
21	M	17	22.28	3.25	19.20	24	1	6
22	M	12	13.96	3.38	31.24	21	1	6
23	F	12	15.43	3.11	20.31	25	1	6
24	M	16	17.26	3.22	30.21	0	1	5
25	F	24	19.69	4.61	48.35	0	2	5
26	M	26	19.66	3.14	25.73	21	1	4

*Cases in which the defect was severe or the chest wall was too rigid, chondral cartilage resection through a midline incision therefore being performed before the metal bar was inserted under the sternum (combined MIRPE + Ravitch technique).

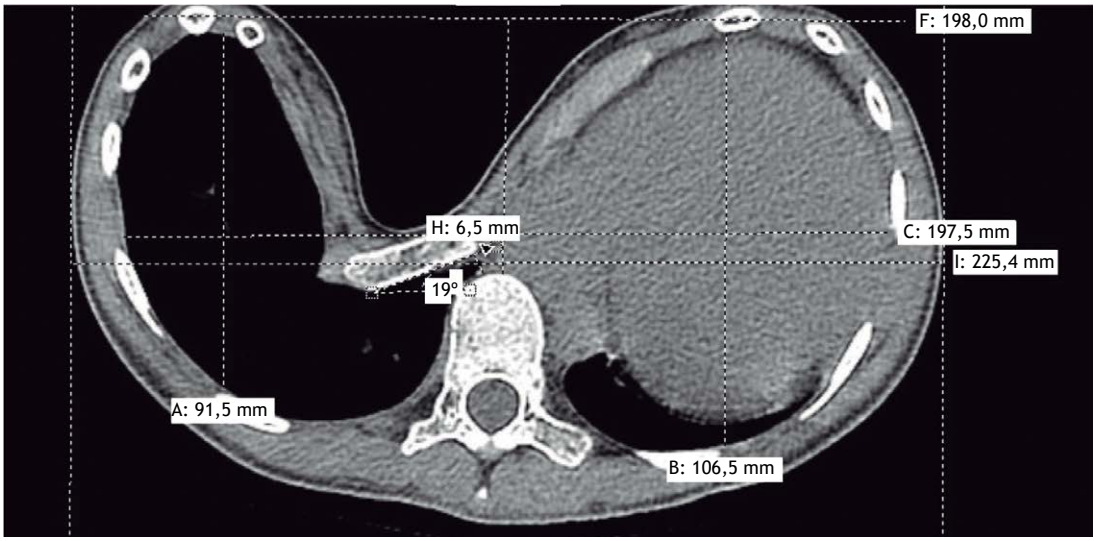

Figure 5. Computed tomography scan of patient 4 (Haller index of 30.3).

of modifications include the left-to-right dissection of the retrosternal tunnel and the use of bilateral thoracoscopy, as well as an approach guided by a specially designed videoscope.[15,21-23] There is a reason for these modifications. Because the heart is dislodged to the left in PE patients, beginning the dissection from this side under left thoracoscopic visualization allows the surgeon to push the pericardium down and simultaneously continue the dissection.

Clearly, what most surgeons propose to avoid cardiac injury is some technique to promote sternal elevation. There are at least two technical modifications that employ newly dedicated devices for sternal elevation, one of which still relies on an additional subxiphoid incision.[19,24] The main problem with those techniques is that these dedicated retractors are usually available only to the group that developed them. There have also been seven reports describing sternal elevation maneuvers that employ non-dedicated devices, including the Kent retractor (Takasago Medical Co., Tokyo, Japan), the Rultract retractor system (Rultract Inc., OH, USA), and the Omni Crane System (Primemed, Seoul, South Korea). Although some are dependent on a complex sequence of steps to grasp the sternum before attaching it to the retractor,[25] others rely on the use of a hook attached to the sternum[26-28] or even the placement of wire sutures into the sternum to complete the elevation.[29,30] Although these crane elevation techniques are celebrated as the safest way of facilitating the creation of the retrosternal tunnel, "grasping" the sternum for elevation is not free of complications. There has been one report of pinpoint perforation of the heart by a needle.[31] Another important consideration is that, even though these maneuvers to elevate the sternum involve the use of what could be called "traditional" retractors, those devices are not available on every surgical ward.

Because it is difficult to become skilled with the pectus introducer and most maneuvers proposed for the retrosternal tunnel creation are based on instruments not always available, we decided to test the feasibility of using only regular instruments during this surgical step. Although thoracoscopic instruments would represent the natural choice for this purpose, which was reserved as a "plan B", and we opted to use truly ordinary surgical instruments. That is why we elected to use the Crawford clamp in this study. Obviously, longer instruments, such as endoscopic tools, can be used instead.

We are not advocating against the use of the pectus introducer. Rather, this study provides preliminary data on a surrogate technique. Although we are aware that this suggestion might seem dispensable for surgeons who are experts in the treatment of PE, the number of cardiac complications reported in literature during the treatment of this benign condition has convinced us to consider alternatives.

This study has some limitations. From a methodological point of view, it would be more appropriate to evaluate two groups: a control group of patients undergoing traditional MIRPE (with the pectus introducer) and another group of patients undergoing MIRPERI. Given that the complication rate of MIRPE is already well reported in the literature and that PE repair is not a common surgical procedure, we choose to show in one case series that the procedure can be accomplished in the way we propose. Another limitation is the small number of patients. However, considering the relative rarity of PE, we believe that 31 is a reasonable number of patients.

In conclusion, our results show that it is possible to dissect a retrosternal tunnel with regular instruments, even in patients with a Haller index as high as 5.6 (e.g., patient 11 in the present study). This technique can serve as an alternative for surgeons who feel unsure about using the pectus introducer. In addition, in this preliminary study of MIRPERI, the complication rates were comparable to those associated with conventional

MIRPE.[4] We believe that the MIRPERI approach, although it seems like a throwback, has the potential to improve the safety of PE repair, particularly for surgeons unaccustomed to the pectus-dedicated instruments or those who do not have access to all of the specific tools required for performing the standard procedure. Studies with larger patient samples are needed in order to confirm our findings.

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REVIEW ARTICLE

Dysfunctional breathing: what do we know?

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ABSTRACT

Dysfunctional breathing (DB) is a respiratory condition characterized by irregular breathing patterns that occur either in the absence of concurrent diseases or secondary to cardiopulmonary diseases. Although the primary symptom is often dyspnea or "air hunger", DB is also associated with nonrespiratory symptoms such as dizziness and palpitations. DB has been identified across all ages. Its prevalence among adults in primary care in the United Kingdom is approximately 9.5%. In addition, among individuals with asthma, a positive diagnosis of DB is found in a third of women and a fifth of men. Although DB has been investigated for decades, it remains poorly understood because of a paucity of high-quality clinical trials and validated outcome measures specific to this population. Accordingly, DB is often underdiagnosed or misdiagnosed, given the similarity of its associated symptoms (dyspnea, tachycardia, and dizziness) to those of other common cardiopulmonary diseases such as COPD and asthma. The high rates of misdiagnosis of DB suggest that health care professionals do not fully understand this condition and may therefore fail to provide patients with an appropriate treatment. Given the multifarious, psychophysiological nature of DB, a holistic, multidimensional assessment would seem the most appropriate way to enhance understanding and diagnostic accuracy. The present narrative review was developed as a means of summarizing the available evidence about DB, as well as improving understanding of the condition by researchers and practitioners.

Keywords: Hyperventilation; Pulmonary ventilation; Respiratory system; Pulmonary medicine.

INTRODUCTION

Dysfunctional breathing (DB) is a respiratory condition that is often poorly understood among health care professionals worldwide, leading to its underdiagnosis and misdiagnosis in clinical practice.[1,2] The reasons for its misdiagnosis include a lack of studies investigating its pathophysiology, classification, and symptoms, as well as the similarity between the symptoms of DB and those of common cardiopulmonary diseases, such symptoms including dyspnea, tachycardia, dizziness, and paresthesia.[3] Misunderstandings about the causes, diagnosis, and treatment of DB appear to indicate that health care professionals do not fully understand this condition and may therefore fail to provide patients with an appropriate treatment, which could lead to impaired health-related quality of life (HRQoL).[4] What is known to date is that DB involves different forms of abnormal breathing patterns,[5] and that it affects approximately 9.5% of all adults in primary care in the United Kingdom.[5] DB has been shown to occur in individuals from 17 to 88 years of age,[2,6,7] being most common in women and in individuals with asthma.[5,8] However, the prevalence of DB can be overestimated or underestimated, given the fact that there is currently no gold-standard tool for diagnosing the condition. Therefore, in this narrative review, we will discuss the definition of DB, as well as the evidence base for its physiological, functional, and psychological characteristics. Our intention is to improve understanding of DB, based on the available scientific evidence, on the part of health care professionals.

DEFINITION AND CLASSIFICATION OF DB

DB is generally characterized by abnormal breathing patterns[4,9] that occur either in the absence of organic diseases (i.e., due to psychogenic causes such as anxiety)[10,11] or secondary to cardiopulmonary/neurological diseases (i.e., due to organic/physiological causes such as asthma and heart failure).[5,12] Jones et al.[6] dubbed the former classification "primary DB" and the latter "secondary DB".[6] It is noteworthy that DB is secondary to organic causes when the physiological alterations are insufficient to explain the evident symptoms (e.g., dyspnea) or the blood gas analysis results.[13] Figure 1 shows a representation of "abnormal breathing patterns". It is important to emphasize that those abnormal patterns can appear with greater recruitment of the accessory muscles of respiration or in cases of chronic respiratory alkalosis.[4,14,15]

In recent years, researchers have proposed some alternative classifications for different patterns of DB. Barker and Everard[4] reviewed the literature and suggested a new definition of DB: "an alteration in the

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normal biomechanical patterns of breathing that result in intermittent or chronic symptoms which may be respiratory and/or non-respiratory". Among the respiratory symptoms listed by the authors were dyspnea and hyperventilation, whereas their list of nonrespiratory symptoms included dizziness and tachycardia. The authors also highlighted the fact that pattern disordered breathing is the main component of any form of DB. Table 1 shows the classifications of DB proposed by various authors. The evident differences across studies regarding the classification of DB and the terminology employed in describing it underscore the need to move from an incipient stage (of discovery) to a more developed phase (of diagnosis and treatment).

The most well-known form of DB is hyperventilation syndrome (HVS), which is defined as acute or chronic hyperventilation (increased minute volume) at rest or during exercise/stress.[16,17] As a form of DB, HVS may be due to organic/physiological conditions but is mainly caused by psychological/behavioral factors (e.g., anxiety, depression, perfectionism, and feelings of inferiority).[16,18] For many years, it was thought that HVS was always accompanied by hypocapnia, which can trigger nonrespiratory symptoms such as dizziness, palpitations, numbness, and a tingling sensation.[19] However, recent studies indicate that such symptoms could be triggered by other, as yet unknown, factors, given that respiratory alkalosis is not always present in HVS.[4,13,20]

There is another form of DB, known as idiopathic hyperventilation (IH), in which patients have chronic asymptomatic hyperventilation and respiratory alkalosis, that cannot be attributed to an underlying disease.[18] Jack et al.[21] showed that IH is mainly caused by psychological factors, becoming a conditioned response. In a subsequent study, Jack et al.[18] hypothesized that IH is caused by increased respiratory responsiveness to carbon dioxide levels, to hypoxia, or to an increase

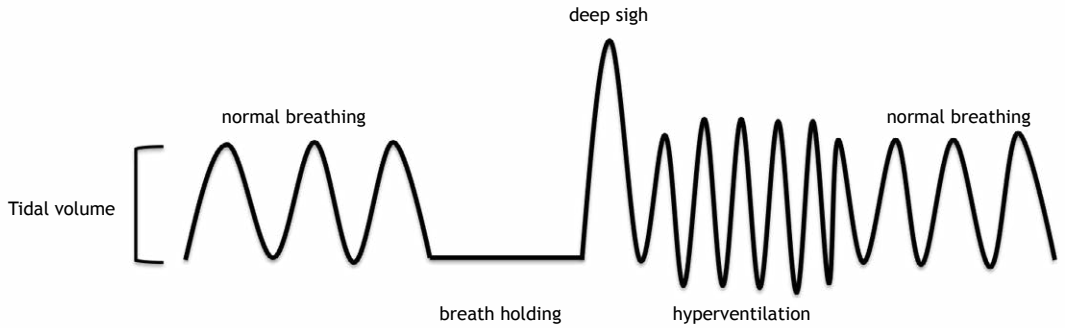

Figure 1. Representative figure showing the "normal" breathing patterns and the "abnormal" breathing patterns presented by individuals with dysfunctional breathing. Normal breathing is the standard tidal volume and respiratory rate of an individual; breath holding is when a breath is held for a period of time; a deep sigh is a deep inspiration that happens at any time during breathing; and hyperventilation is an increase in the respiratory rate, tidal volume, or both. Note: The order in which abnormal breathing patterns appear may vary.

Table 1. Recent classifications of dysfunctional breathing suggested by different authors.

Authors Classification	Definition
Boulding et al.[9]	
Hyperventilation syndrome	Related to respiratory alkalosis or independent of hypocapnia
Periodic deep sighing	Usually associated with an irregular breathing pattern
Thoracic dominant breathing	Can manifest more often in somatic diseases
Forced abdominal expiration	Evident when there is inappropriate and excessive abdominal muscle contraction during expiration
Thoracoabdominal asynchrony	Characterized by a delay between intercostal and abdominal contraction, causing ineffective respiratory mechanics
Barker and Everard[4]	
Thoracic DB	Significant changes in the breathing pattern that may or may not be directly linked to hyperventilation
Extrathoracic DB	Upper airway impairment manifested in combination with breathing pattern disorders (e.g., vocal cord dysfunction)
Functional DB (a subdivision of thoracic and extrathoracic DB)	No structural or functional alterations directly associated with the symptoms of DB (e.g., phrenic nerve palsy, myopathy, and diaphragmatic eventration)
Structural DB (a subdivision of thoracic and extrathoracic DB)	Primarily associated with anatomical or neurological alterations (e.g., subglottic stenosis and unilateral cord palsy)

DB: dysfunctional breathing.

in the metabolic rate, although that hypothesis has not been tested.

DIAGNOSIS OF DB

Nijmegen Questionnaire

Currently, the Nijmegen Questionnaire (NQ) is the most widely used instrument for identifying individuals with DB.[22,23] The NQ was developed by van Dixhoorn and Duivenvoorden in 1985.[23] Although the authors did not specify whether the participants had primary or secondary HVS, they mentioned the exclusion of participants with somatic disorders, which would suggest the exclusion of those with primary DB. Nevertheless, they included no information on whether any of the participants had a history of asthma or other health conditions.

The NQ consists of 16 questions related to complaints, and the frequency of symptoms can be indicated on a scale ranging from 1 (never) to 5 (very often). It has a sensitivity and specificity of 91% and 95%, respectively, in relation to the clinical diagnosis of HVS. The questions are primarily related to physiological factors (e.g., cardiovascular and respiratory symptoms) and psychological factors (e.g., tension). However, it is noteworthy that this instrument was developed as a symptom-based questionnaire to screen for HVS.[23] In fact, the NQ has been validated only for use in patients with HVS secondary to asthma (i.e., not for use in those with other forms of DB).[24] In addition, the NQ has yet to be translated to Portuguese or validated for use in Brazil. In a recent article, one of the creators of the NQ stated that it has been used incorrectly worldwide,[25] stating that it should be used only to identify abnormal symptoms related to HVS and not as the gold-standard test to diagnose DB per se, because it was not created for that purpose. However, given that HVS was the first form of DB to be investigated and is still the most well understood form of the condition, several tools, other than the NQ, have been developed to facilitate the identification of hyperventilation (as described below).

The hyperventilation provocation test to identify HVS

The hyperventilation provocation test (HVPT) was once considered to be the cornerstone of the diagnosis of HVS.[26] The HVPT requires patients to breathe as deeply and quickly as possible for a certain length of time (typically 2 or 3 min). To determine whether patients have HVS, the authors who developed the HVPT suggested that clinicians check patient reports of symptoms and experiences during the test. If a patient reports symptoms and sensations that are similar to those experienced regularly in their daily lives, the presence of HVS can be confirmed.[27] However, a number of researchers have begun to question whether the HVPT is a valid tool to detect HVS, because it does not differentiate between symptoms caused by hypocapnia and those caused by task-related anxiety or mechanical discomfort.[28] In such instances, the HVPT is highly likely to overestimate the prevalence of HVS.[13,28] In addition, a delay for blood CO_2 levels to return to baseline values after an HVPT was once believed to be diagnostic of HVS.[27] However, it was later shown that the length of the delay in CO_2 recovery does not differ between patients with HVS and healthy individuals.[28]

Cardiopulmonary exercise testing to identify HVS

Another means of facilitating the diagnosis of HVS is cardiopulmonary exercise testing.[18,20] Such testing has been recommended when patients do not experience HVS-related symptoms at rest but health care professionals suspect that, based on patient reports, these sensations are likely to occur during movement.[18,20] That assumption is predicated on compelling evidence indicating that, on incremental cycle ergometer tests, individuals with chronic IH show lower end-tidal CO_2 tension, higher minute volume, slower recovery, and a higher degree of dyspnea (disproportionate to the increase in minute volume), as well as supporting lower workloads, than do healthy individuals.[18,20,21] Although the use of cardiopulmonary exercise testing might also facilitate the exclusion of other causes of dyspnea,[29] the protocol for the identification of HVS during cardiopulmonary exercise testing has yet to be standardized. Therefore, exercise tests appear to be complementary tools that can facilitate the detection of HVS in more complex situations, in which patients do not show any of the aforementioned symptoms at rest.

PHYSIOLOGICAL CHARACTERISTICS OF DB

Pulmonary function

Although pulmonary function test parameters, such as FEV_1 and FVC, are widely used to classify respiratory diseases, they do not seem to distinguish patients with DB. Data in the literature describing pulmonary function in DB are extremely divergent.[30,31] There is compelling evidence that individuals with primary DB have normal lung function,[1,2,17,30] whereas other studies have shown that FEV_1 or FVC are 10-15% below the predicted values in such individuals.[17,31] In addition, Agache et al.[32] showed that FEV_1 declined faster over a 12-month period in patients with asthma-induced DB (secondary DB) than in those with asthma alone. Furthermore, Jones et al.[6] reported that a 26-week breathing retraining program improved FEV_1 in patients with primary DB. These findings can be explained by the fact that some patients with DB hyperventilate, which causes hypocapnia, accompanied by reduced airway caliber and increased airway resistance.[33,34] It is well established that, when trial data are reported, pulmonary function test results should be provided as raw data (in L or mL) and as percentages of the predicted values, with the use of reference equations that are specific to the studied population.[35] However, most

authors investigating DB (either primary or secondary) have evaluated changes in lung function by analyzing only raw data and not percentage data.[1,2,17,30-32] Others have presented the data as percentages of the predicted values without indicating the reference equations used in their calculation.[17,30-32]

Courtney et al.[30] used spirometry to assess pulmonary function in a mixed group of healthy individuals and individuals with mild medical conditions (including suspected DB). Following the pulmonary function tests, participants were divided in two groups, on the basis of the results of those tests: normal and abnormal. The authors found that, in comparison with the participants who showed normal lung function, those with abnormal lung function had lower blood CO_2 levels, shorter breath-holding times, and lower oxygen saturation, as well as scoring higher (i.e., worse) on the Self-Evaluation of Breathing Questionnaire.[30] These results suggest that there is a group of patients with DB and chronic hyperventilation (and therefore hypocapnia) who have abnormal lung function. Therefore, it seems that any conclusion regarding pulmonary function in DB can be considered an attempt to simplify the multifaceted phenomena seen in individuals with DB.

It is important to emphasize that researchers and health care professionals should not expect to find substantially abnormal spirometry results in individuals with primary DB, because it is not considered a respiratory disorder. Despite the fact that hypocapnia has an influence on airway caliber (i.e., constricts the airways),[33,34] not all patients with DB exhibit hyperventilation. Therefore, the reported degree of pulmonary function impairment varies widely across studies of DB, which justifies attempts to investigate this parameter in greater depth.

Respiratory muscle function

A number of studies have demonstrated abnormal function of the respiratory muscles (e.g., hyperventilation),[1,11,36] with or without greater recruitment of the accessory muscles of respiration, in patients with primary DB.[6,31,37] In healthy individuals, common situations such as emotional stress cause predominantly thoracic breathing, muscle tension, and increased respiratory muscle effort.[38] When such symptoms are persistent and have no physiological cause, they are suggestive of DB.[36] The accessory muscles of respiration also provide postural control and facilitate breathing during stressful situations, exercise, or threatening situations.[39,40] Emotional stress and anxiety cause abdominal muscle tension, which inhibits diaphragmatic movement. That can induce thoracic breathing and greater recruitment of the accessory muscles of respiration,[6,41] resulting in dyspnea,[42,43] increased work of breathing,[11] and respiratory muscle fatigue.[44]

In various respiratory conditions (e.g., COPD and asthma), the degree to which the accessory muscles are recruited indicates the severity of the disease.[45,46] The accessory muscle recruitment caused by psychological conditions frequently associated with DB could result in general muscle tenderness, especially in the upper chest, shoulders, and neck.[47] In addition, some patients with DB exhibit audible, forced expiration,[47] which could be indicative of inappropriate expiratory muscle activation at rest. Many authors have speculated on whether or not respiratory muscle function (RMF) is impaired in patients with DB.[48] Therefore, there seems to be insufficient evidence in the literature to support a positive or negative theoretical position regarding respiratory muscle dysfunction as a feature of DB.

The existing literature indicates that RMF in DB has primarily been evaluated by measuring the breathing pattern at rest as a means of identifying thoracic/paradoxical breathing, through the use of techniques such as manual assessment of respiratory motion.[36,37] However, measurements of breathing pattern performed at rest provide no objective information regarding the contractile properties of the respiratory muscles. The manual assessment of respiratory motion technique has been shown to have better inter-rater reliability and validity than does respiratory inductance plethysmography[49] and is considered a valuable tool in the clinical field, where practitioners have limited access to laboratory equipment. However, more robust physiological measures of RMF, such as muscle strength, endurance and mechanical power, should also be considered in this population.[50]

According to Agache et al.,[32] the treatment for DB frequently includes strengthening the diaphragm muscle. However, in the present review, we identified no studies applying respiratory muscle training in DB. In addition, there is no evidence to support the idea that RMF is impaired in patients with DB; nor is there any evidence that inspiratory muscle training has beneficial effects in this population. It is possible that patients with primary DB develop dynamic hyperinflation during hyperventilation, which would impair RMF by shortening and weakening the muscles. However, that theory remains untested. Given the paucity and inconclusive nature of the data currently available,[32,50] we highly recommended the direct assessment of RMF.

Cardiopulmonary interactions

Respiration exerts a potent influence on the autonomic system.[51] Slow, controlled breathing (≈ 6 breaths/min) increases the amplitude of respiratory sinus arrhythmia (RSA), which is a time-domain index of heart rate variability (HRV).[52] In addition to being a robust index of HRV, RSA is a complex physiological phenomenon; the function of which has yet to be fully understood. The amplitude of RSA (and therefore HRV) decreases during tachypneic or erratic breathing patterns. Patients with COPD show lower HRV,[53] which could be attributed to their abnormal breathing pattern. Furthermore, low HRV has been associated with negative prognostic indicators in a number of patient populations (e.g., patients with COPD and patients on hemodialysis).[54,55] Accordingly, given the well-established synchrony between the respiratory and

cardiovascular systems,[51] it is likely that, in patients with DB, cardiovascular activity is atypical (e.g., an altered pattern of arterial blood pressure and HRV). Therefore, if a patient with DB is taught to breathe in a controlled manner, at a lower respiratory rate, sympathetic activity can be attenuated,[52] a physiological mechanism that could optimize/facilitate gas exchange and mitigate the symptoms of DB.

Courtney et al.[56] detected a significant relationship between a predominantly thoracic breathing pattern and HRV indices that reflect cardiopulmonary efficiency in patients with DB. In the past, it has been argued that hyperventilation is a major cause of cardiac symptoms, due to the cerebral and peripheral vasoconstriction occurring secondary to hypocapnia.[26] It has been suggested that the underlying mechanism is hyperventilation and the consequent hypocapnia, which suppresses sympathetic and parasympathetic activities, the greatest decrease being observed in the parasympathetic activity in the heart.[4,57] Hyperventilation also induces a reduction in cerebral blood flow as a result of hypocapnia; this mechanism is likely to account for the symptoms commonly reported in patients with DB, such as dizziness and unsteadiness.[47] Although there are psychophysiological reactions associated with DB, it remains unclear whether episodes of irregular breathing pattern have an influence (direct or indirect) on the autonomic nervous system.

Gas exchange and ventilation

It has been suggested that patients with DB expend more energy at rest because of their irregular breathing pattern,[11] which could be explained by anxiety-related factors and increased respiratory muscle work. However, Malmberg et al.[58] showed that, when the participants were in the supine position, gas exchange variables were similar between the patients with HVS and healthy individuals. Nevertheless, when the participants were in a standing position, the patients with HVS had lower levels of expired CO_2 and higher minute ventilation (V_E), as well as higher ventilatory equivalents for oxygen (V_E/oxygen uptake), carbon dioxide (V_E/carbon dioxide production), oxygen (minute volume/oxygen uptake), and CO_2 (minute volume/carbon dioxide production), than did the healthy individuals. In addition, Jack et al.[18] reported that patients with IH (i.e., hyperventilation associated with low carbon dioxide production, unrelated to other diseases and not associated with fear) exhibit sustained hyperventilation, higher dyspnea, and lower ventilatory responsiveness to hypoxia during an incremental cycle ergometer test, in comparison with healthy individuals. However, the authors found that those same patients showed variable energy expenditure levels, as well as normal responses to hypoxia and normocapnia at a higher CO_2 level (40 mmHg). Therefore, the energy expenditure and ventilation levels of patients with DB have hitherto been under-researched. Those components are of great relevance to furthering understanding of this respiratory condition and should not be overlooked during the collection, analysis, and interpretation of data.

FUNCTIONAL CHARACTERISTICS OF DB

Functional assessments

In patients with DB, functional assessments (e.g., breath-holding tests and visual evaluation of breathing patterns) are commonly used in order to complement the identification of this respiratory condition.[17] However, there is little evidence of any strong correlations between these functional outcomes and the underlying physiological parameters.[17,56] There is also insufficient evidence to support direct correlations between functional outcomes and the score on the NQ.[24,31,36] In addition, there are no validated tools specifically designed to assess individuals with DB.[31]

In 2011, Courtney et al.[17] investigated a group of individuals who had concerns about their breathing but had not received a diagnosis of primary or secondary DB. The authors identified weak to non-existent correlations among biochemical indices (e.g., lower end-tidal CO_2 tension), breath-holding time, and symptom-related questionnaire scores. In a more recent study, involving patients with primary HVS, quality of life (QoL) measurements (domains of the Medical Outcomes Study 36-item Short-Form Health Survey) were found to correlate moderately with NQ scores, peak respiratory rate, and end-tidal CO_2 tension during cardiopulmonary exercise testing.[59] As was evident in the aforementioned studies, there is as yet insufficient evidence of correlations between functional parameters and DB-related symptoms and there is a need for further investigation. Future studies should also aim to recruit a larger number of patients with DB in order investigate the influence of DB on function-related tasks, such as the breath-holding test.

Exercise capacity

Exercise capacity is a parameter commonly affected by respiratory diseases such as COPD and cystic fibrosis.[60,61] However, there have been few studies employing exercise capacity tests and performing physiological/psychological assessments during exercise in patients with DB, and the few that have been conducted have produced controversial results. Such studies typically recruit patients with HVS or secondary DB, as described below. Some studies have also employed progressive exercise tests to confirm the diagnosis of HVS, as identified by the presence of hyperventilation during exercise and at rest, in patients with asthma.[20]

Warburton and Jack[20] suggested that cardiopulmonary exercise testing is the most sensitive tool to confirm the diagnosis of HVS, which can be established when patients hyperventilate during exercise performed during exercise activities, such as running and cycling. However, it remains unknown whether exercise performance outcomes or variables collected during exercise are somehow useful in the assessment of

other forms of DB. Chenivesse et al.[59] employed maximal cardiopulmonary exercise testing on a cycle ergometer in patients with HVS and recorded a range of respiratory variables.[59] The authors found that the patients with HVS showed exercise-related impairments (e.g., aerobic capacity below 84% of the predicted value) and hyperventilated not only at rest but also (and perhaps even more) during exercise. We find it interesting that most of the patients with HVS in that study showed normal changes in the breathing pattern and a normal increase in respiratory rate, as well as normal cardiovascular responses, during maximal cardiopulmonary exercise testing. However, it is noteworthy that the authors compared their results with those of other studies investigating healthy participants; in other words, there was no direct comparison between patients with HVS and healthy individuals in their study.

Howell[13] suggested that symptoms of HVS occur predominately at rest but can occur during exercise, proposing that such symptoms are not directly associated with the intensity of the exercise performed.[13] Jack et al.[21] systematically investigated that proposition and found it to hold true. In the latter study, a group of patients were observed to hyperventilate prior to or at the onset of the exercise test, a psychological condition dubbed anticipatory anxiety.[62] In such instances, patients tend to hyperventilate when facing a challenging situation. It is noteworthy that there is also a subcategory of individuals with chronic hyperventilation who show appropriate changes in CO_2 from rest to exercise or from rest to sleeping and possess exercise capacity similar to that of healthy participants. Therefore, Jack et al.[21] suggested that psychological variables such as anxiety-related factors should be assessed in this population, not only at rest but also in exercise-related situations.[21] More recently, Courtney et al.[17] argued that, when measurements of CO_2 at rest are not suggestive of DB, CO_2 should be measured during an exercise test, in a challenging situation (e.g., retrieving an old memory), or both. Similarly, Hagman et al.[1] identified breathing difficulties during exercise in patients with DB and in patients with asthma. In a subsequent study, the same group of authors found that a one- to three-month breathing retraining program ameliorated breathing difficulties during exercise.[2] Notably, that improvement was maintained over a 5-year follow-up period. There is a need for systematic studies assessing exercise capacity, as well as physiological and psychological changes during exercise, in patients with primary DB. Given that HVS is a subcategory of DB and appears to have a negative effect during exercise, it is extremely relevant that the results of exercise capacity tests are taken into consideration when patients are suspected of having DB. Evaluation of individuals during exercise sessions or other stressful situations to diagnose DB could provide health care professionals with a broader, richer, and more nuanced perspective of the nature of the condition, as well as facilitating/expediting its diagnosis and treatment.

PSYCHOSOCIAL CHARACTERISTICS OF DB

Anxiety and depression

Although respiratory and cardiovascular parameters undergo significant changes in emotionally challenging situations (i.e., the "fight-or-flight response" occurs) in all individuals, patients with DB commonly experience abnormal psychophysiological responses when facing similar scenarios.[9] DB induces significant changes in the respiratory rate, breath-holding time, and depth of breathing that are primarily mediated by current or previous traumatic experiences or psychological conditions (e.g., anxiety). These symptoms may also occur chronically, which leads to deterioration of the QoL of the individual.[11,63] Accordingly, a strong correlation between psychological condition and changes in normal breathing has been identified in different contexts (e.g. during musical performances) in healthy individuals.[64] Anxiety and depression are common among patients with HVS.[10,21,47,65] In fact, Hagman et al.[1] showed that the addition of DB to asthma (secondary DB) is associated with higher levels of anxiety and depression. However, the incidence of anxiety/depression in DB and whether such disorders are essential factors in the identification of DB remain unclear and require further research.

QoL

Some authors have suggested that symptoms of DB secondary to asthma can influence HRQoL, as determined by the Asthma Quality of Life Questionnaire and the Medical Outcomes Study 36-item Short-Form Health Survey, two well-established tools for the assessment of HRQoL.[66,67] Hagman et al.[1,2] and Chenivesse et al.[59] assessed QoL in individuals with primary HVS and found that HRQoL was lower in those individuals than in groups of healthy participants. Hagman et al.[2] also proposed that breathing retraining had a positive effect on QoL even at the end of a 5-year follow-up period. However, a Cochrane systematic review investigating treatment for DB identified only one randomized controlled trial (RCT) in this field of research, and that trial did not include an assessment of QoL.[15] Given that DB may be associated with impaired QoL, it is crucial to gain greater insight and understanding of the impact that DB has on this parameter. Therefore, we believe that further research should be conducted in order to elucidate the psychophysiological and behavioral mechanisms that underlie DB. By identifying such triggers, clinicians are more likely to provide patients with an appropriate and effective treatment that will have various positive consequences on QoL.

TREATMENT OF DB

There are few data in the literature regarding treatment for patients with DB. That paucity can be explained by differences across studies in terms of the recruitment methods employed, which is understandable because that there is no standardized diagnostic tool available for DB. Therefore, it is extremely important to

be cautious when considering these results in research or clinical practice.

In 2013, Jones et al.[15] published a systematic review looking at RCTs in which DB was treated with breathing exercises and the effects that those exercises had on patient QoL were evaluated. The authors identified only one such RCT, conducted in the Netherlands,[68] in which 41 patients with HVS were evaluated. In that study, there were two intervention groups (relaxation therapy only and relaxation therapy plus breathing exercises) and a control group. The relaxation therapy was based on a combination of yoga techniques and the method devised by Jacobson.[69] The breathing exercises focused on reducing the respiratory rate and encouraging diaphragmatic breathing. Both intervention groups were treated in ten 60-min sessions. The study had two main outcome measures: the number and intensity of hyperventilation attacks; and the symptoms experienced. However, the authors did not specify how those parameters were assessed. The results show that there was a significant reduction in number and intensity of hyperventilation attacks in both intervention groups in comparison with the control group, the patients in the relaxation therapy plus breathing exercises group improving more than did those in the relaxation therapy-only group.

Apart from the abovementioned RCT, the main therapeutic approach utilized for patients with DB is breathing retraining.[2,6] In 2003, Thomas et al.[66] found that patients with DB secondary to asthma showed significant symptom improvement after breathing retraining. In 2011, Hagman et al.[2] concluded that patients with DB benefit from breathing retraining, even at the end of a 5-year follow-up period. In 2015, Jones et al.[6] found that manual therapy does not add benefit to breathing retraining in the same population. However, the differences among recruitment methods, as well as among breathing retraining programs, and the lack of descriptions of protocols show the need for further clinical trials in this field of research.

FINAL CONSIDERATIONS

Due to the multifaceted, complex nature of DB, a holistic multidimensional assessment is required for the accurate diagnosis of this respiratory condition. That being the case, three key domains—biochemical aspects, biomechanical aspects, and respiratory symptoms—require further investigation in order to improve our understanding of DB.[17,25] In addition, based on our critical analysis of the existing literature, we believe that psychological, social, and physiological domains also have a significant impact on the pathology and severity of DB (Figure 2). Finally, treatment for patients with DB needs to be better investigated, not only because of the lack of a diagnostic tool that would enable consistent recruitment of participants but also because of the scarcity of RCTs testing well-defined protocols for this patient group.

The lack of studies investigating the respiratory symptoms of DB, as well as its biochemical, biomechanical, psychological, social, and physiological aspects, perpetuates poor understanding and often results in delayed diagnosis of the condition. Therefore, the development of a multidimensional assessment tool specifically for DB, as well as a set of standardized clinical outcome measurements to identify and monitor treatment efficacy, are essential prerequisites to improving the provision of effective health care services for individuals with DB.

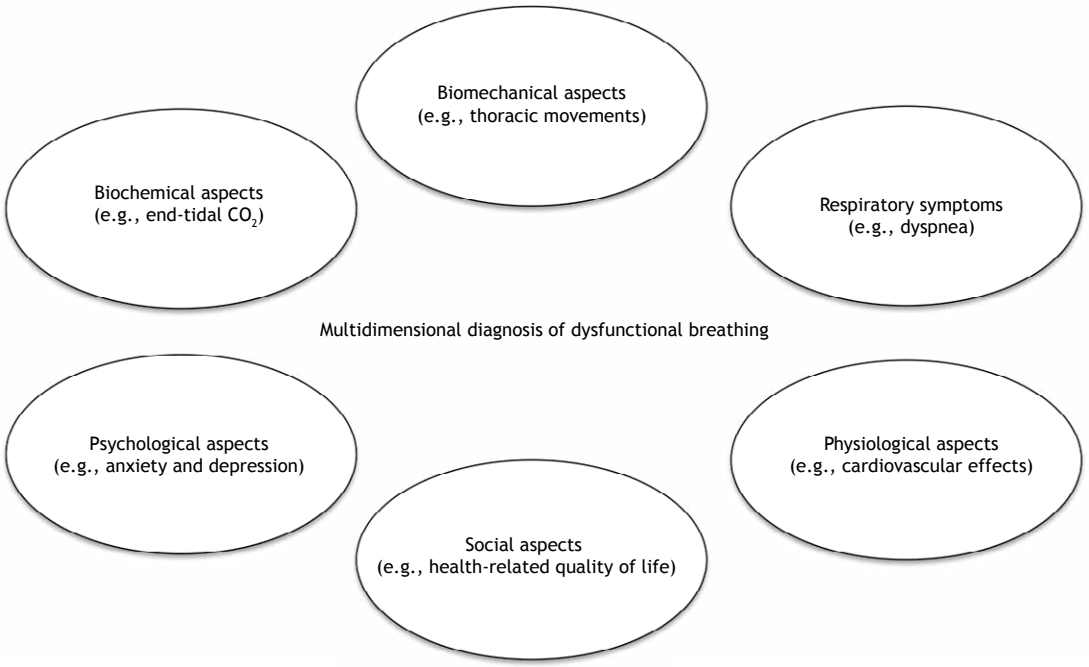

Figure 2. Representative diagram of the proposed aspects involved in the multidimensional diagnosis of dysfunctional breathing.

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Pleural effusion caused by infection with *Listeria monocytogenes*: etiopathogenesis and treatment

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TO THE EDITOR:

Listeria monocytogenes is a gram-positive rod that is commonly found in soil, water, and the fecal flora of many mammals.[1] In at-risk groups, including neonates, pregnant women, and elderly individuals, and immunocompromise individuals, such as those with underlying malignancies, those receiving immunosuppressive therapy, and those infected with HIV, the most common presentations of *L. monocytogenes* infection are sepsis and meningitis.[2,3] Pleural infection by this pathogen is extremely rare.[1-7] Only approximately 20 such cases have been reported, most of those were in immunocompromised patients with hematologic malignancies,[3,6,8] although at least three cases have been reported in patients with liver cirrhosis.[2,3]

A 63-year-old woman, previously diagnosed with Evans syndrome (treated chronically with 5 mg/day of methylprednisolone), class III obesity with marked lipodystrophy, heart failure, and autoimmune hepatitis-related cirrhosis, presented to our hospital with a five-day history of right pleuritic chest pain and shortness of breath. At presentation, she was afebrile. Physical examination revealed diminished breath sounds over the lower two-thirds of the right chest. Laboratory tests showed normocytic normochromic anemia (hemoglobin of 9.9 g/dL), leukocytosis (14.8 × 10^3 leukocytes/μL), thrombocytopenia (78 × 10^3 cells/μL), C-reactive protein level of 18 mg/dL, lactate dehydrogenase of 156 U/L, creatinine of 1.6 mg/dL, gamma-glutamyl transpeptidase of 155 U/L, alkaline phosphatase of 153 U/L, hypoalbuminemia (serum albumin of 2.4 g/dL), and negative serology for HIV. A chest X-ray showed right pleural effusion of moderate volume (Figures 1A and 1B). The patient was admitted to the hospital for etiological investigation of the pleural effusion.

Diagnostic ultrasound-guided thoracentesis was carried out. Analysis of the pleural fluid revealed exudates with a pH of 7.3, 5.7 g/dL of proteins, 45 mg/dL of glucose, 324 U/L of lactate dehydrogenase, and an abnormal complete blood count (abundance of erythrocytes). There was no malignancy, Ziehl-Neelsen staining was negative, and gram staining was positive. A chest tube was inserted and connected to an underwater seal drainage system, which yielded bloody fluid. *L. monocytogenes* was isolated from a culture of the pleural fluid and from blood cultures, although not in a culture of cerebrospinal fluid aspirate. Neither ascites nor neurologic manifestations were present, although there have been reports of peritonitis and meningoencephalitis accompanying pleural effusion caused by *L. monocytogenes* infection. The patient also underwent CT scans of the brain and abdomen, neither of which showed any acute abnormalities. There was no relevant epidemiological context in her community. A second culture of pleural fluid was positive for *L. monocytogenes*, thus confirming the previous results. A CT scan of the chest showed massive right pleural effusion (Figure 1C).

The initial treatment was intravenous ampicillin (2 g every 4 h) and adjuvant oral trimethoprim-sulfamethoxazole, based on evidence in the literature. After 7 days, the patient developed myelotoxicity and the trimethoprim-sulfamethoxazole was therefore replaced with gentamicin. The patient completed 14 days of treatment, which resulted in favorable clinical and radiological responses.

It should be noted that our patient had chronic liver disease and was under treatment with an oral corticosteroid, two conditions that could have been predisposing factors for invasive listeriosis.[2,3] Although there is no consensus regarding the mechanism by which *L. monocytogenes* enters the pleural cavity, hematogenous spread and subsequent seeding to the pleura was the most probable route of infection in the case presented here.

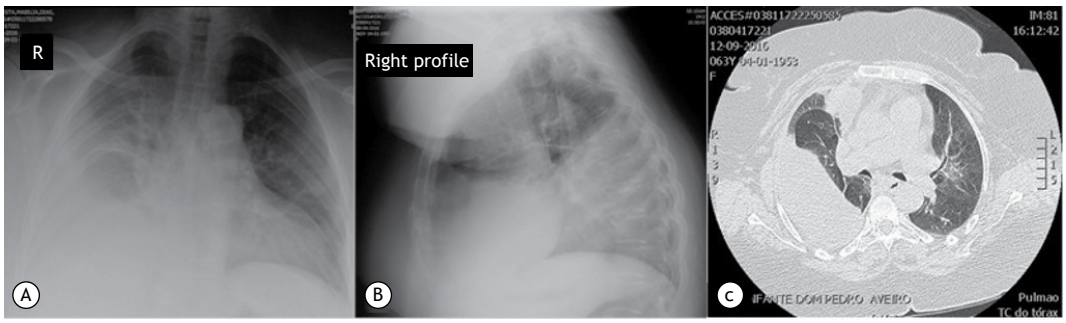

Figure 1. Chest X-ray in posteroanterior and right lateral views (A and B, respectively), showing right-sided pleural effusion. A CT scan of the chest (in C), showing massive right-sided pleural effusion.

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A case series involving nine patients reported an overall mortality rate of 44.4%,[6] and mortality appeared to be lower for the patients who were treated with an aminoglycoside combined with penicillin or ampicillin and for those who underwent drainage of pleural fluid.[1,2,6,7] Because of the small number of cases, the prognosis for patients with pleural effusion caused by *L. monocytogenes* infection is unknown, although rapid diagnosis, prompt institution of appropriate antimicrobial therapy, and effective drainage of pleural fluid are likely to improve chances of survival.[1,2,6]

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Probe-based confocal laser endomicroscopy of the airways: physiological and pathological characteristics of preneoplastic and neoplastic lesions

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TO THE EDITOR:

Primary lung cancer has a high incidence and high mortality, with a five-year survival rate of 10-15%. That is because most patients are diagnosed at advanced stages of the disease. Various imaging methods and histological sampling methods have been developed to enable earlier and more precise diagnosis of lung cancer.[1]

Although it is feasible to obtain airway tissue samples via bronchoscopy, there is great interest in researching methods that will allow in vivo microscopic visualization of tissue structure. That is because of the constant need to differentiate malignant or premalignant lesions from the normal mucosa, making it possible, if not to establish a diagnosis, then to guide biopsy to ensure that the sample collected is representative of the lesion.

The advent of lasers led to the development of an imaging technique known as probe-based confocal laser endomicroscopy (pCLE), which uses a miniprobe (containing thousands of optical fibers and connected to a laser light source) to analyze small areas of tissue, allowing microscopic changes (in the mucosa and other tissues) to be assessed.[2] Some studies have defined the characteristics of endomicroscopy images of airway structures (such as the trachea, bronchi, and alveoli), as well as those of certain diseases (such as some types of lung cancer).[3]

One pCLE system currently on the market is the Cellvizio system (Mauna Kea Technologies, Paris, France), which uses a wavelength of 488 nm: images result from autofluorescence of subepithelial elastin fibers in the bronchial mucosa, which account for more than 50% of airway support tissue.

A prospective study of four cases was conducted at the University of São Paulo School of Medicine *Hospital das Clínicas*. The study was approved by the local research ethics committee (Protocol no. 315/13).

The patients evaluated were suspected of having centrally located lung cancer, information that is important for access to the tumor under direct visualization and correct positioning of the miniprobe, which should be in contact with the lesion. Of the four patients, two were male. Three of the patients were smokers (mean smoking history, 58 pack-years). The following histological types were identified: adenocarcinoma, in two; and squamous cell carcinoma, in two. Initially, we used endoscopy (flexible bronchoscopy) to assess the entire airway, identifying any visible changes. We then inserted the pCLE miniprobe into the working channel of the bronchoscope, positioning the miniprobe sequentially over normal mucosa of the tracheobronchial tree and lung parenchyma, subsequently placing it on the surface of the tumor. Figure 1 shows an example of endoscopic visualization of the pCLE miniprobe and identification of a lesion in the orifice of the right upper lobe.

The literature suggests that analysis of pCLE images allows identification of five patterns of distribution of elastin fibers in the airway submucosa.[4] These patterns vary according to their location in the airway, and, even in our initial experience, it was possible to identify these five patterns in all cases studied: in the trachea, carina, and main bronchi, elastin fibers are parallel to each other, forming a single longitudinal layer (Figure 2A); in the secondary carina, elastin fibers are parallel to each other in layers, which are distinguished by the orientation of the fibers. At that time, it was also possible to perceive the orifice between the bronchial gland and the airway (Figure 2B); in the segmental and subsegmental bronchi, there is greater rarefaction of the elastin fibers, which begin to interlace with the underlying layers (Figure 2C); in the distal bronchioles, the network of interlaced elastin fibers of the bronchi assumes a helical conformation, culminating in the formation of a network of support for the alveolar bronchioles (Figure 2D); and the alveolar bronchioles and alveoli are represented by an elastin fiber network that expands and forms a three-dimensional support framework, comprising structures such as sacculations for the support of the alveolar cells and capillaries (Figure 2E).

In addition to the normal patterns, we visualized changes in the alveoli of the patients who smoked, marked by alveolar filling with inflammatory cells (Figures 2F and 2G), well as changes in the pulmonary parenchymal architecture in peripheral areas of the tumor, characterized by alveolar wall thickening secondary to an increase in the elastin bundle diameter, alveolar edema, and a

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large number of macrophages in the alveolar space (Figures 2H and 2J).

In the cases of adenocarcinoma, it was possible to see, in the tumor area, an amorphous mass filling the alveolar space and destroying its wall, characterized by alternating areas of high fluorescence, due to the misshapen aggregate of elastin, and dark cavities, representinglarge blocks of tumor cells, which are not autofluorescent (Figures 2K and 2M). In contrast, in the cases of squamous cell carcinoma, we saw an amorphous mass with branches that were less fluorescent, thicker, and more numerous, representing stroma, as well as dark layers representing the cellular component (Figures 2N and 2O).[5]

On the basis of knowledge of the usual distribution of elastin fibers in each airway segment, studies

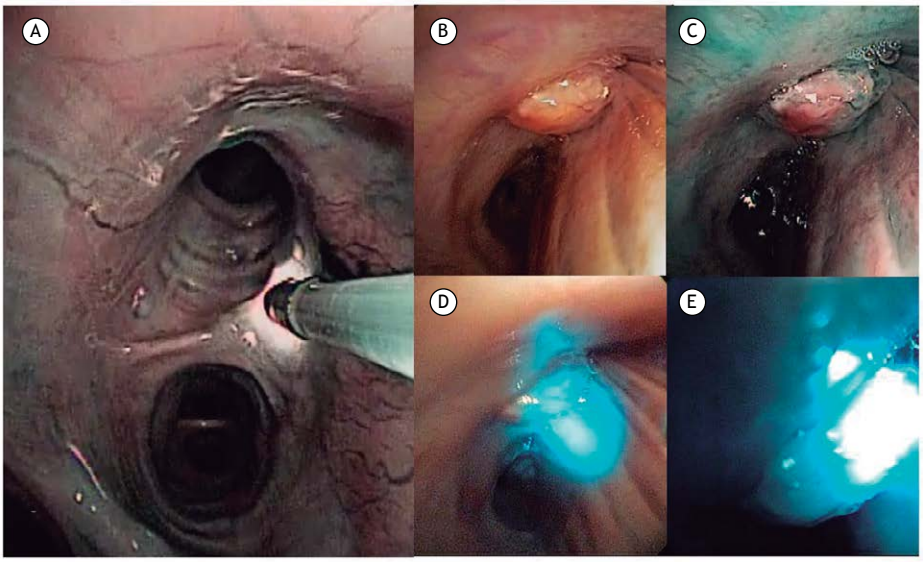

Figure 1. In A, endoscopic visualization of the confocal endomicroscopy miniprobe; in B; white-light endoscopic image of a neoplastic lesion; in C, narrow-band image of a neoplastic lesion; in B, illumination by the laser light source in the airway; and in E, contact of the miniprobe with the laser light source for generation of confocal endomicroscopy images.

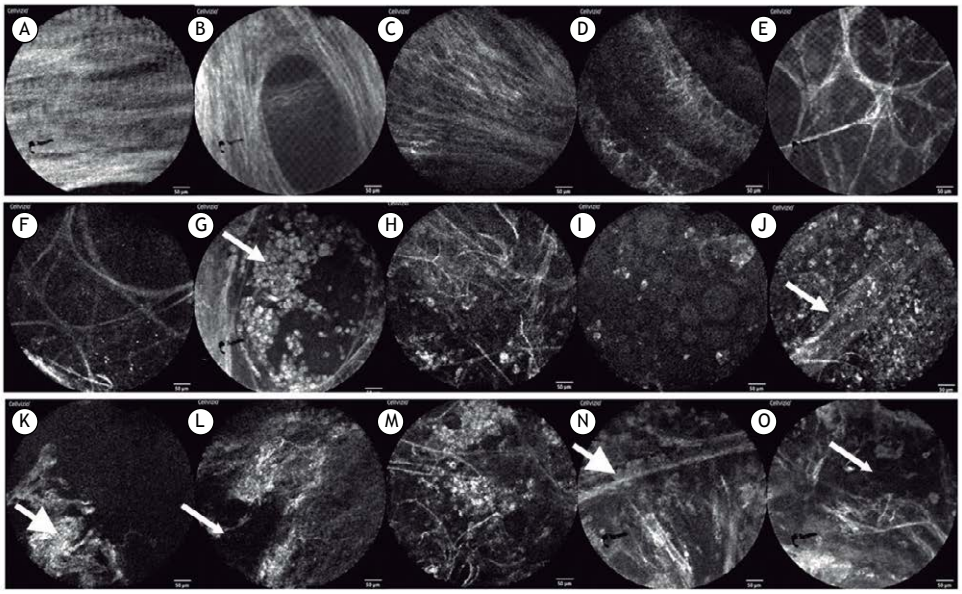

Figure 2. Distribution of elastin fibers in the airways. In A, trachea; in B, bronchial gland; in C, segmental bronchus; in D, distal bronchiole; and, in E, alveoli. Normal alveolar pattern and changes seen in the patients who smoked: in F, normal alveolar architecture; and, in G, pulmonary alveoli filled with inflammatory cells and alveolar macrophages (arrow). Inflammatory changes in the area surrounding the tumor: in H, alveolar wall destruction associated with disorganized proliferation of elastin fibers, as well as elastin fiber thickening; in I, alveolar edema, caused by filling of the alveolar space with fluid; and, in J, a large quantity of cells in the alveoli, making it possible to visualize an alveolar capillary (arrow). Changes in the tumor: in K, L, and M, a hyperfluorescent aggregate of elastin (large arrow) alternating with a dark area corresponding to a neoplastic cell conglomerate (small arrow); and, in N and O, an amorphous, less autofluorescent mass (stroma: large arrow), alternating with a dark area of hypercellularity, and tumor cell conglomeration (small arrow).

have been carried out to standardize the changes in these structures, comparing them with those in samples obtained from surgical specimens, and thus correlate them for the in vivo diagnosis of malignant and premalignant lesions.[6]

It is believed that pCLE is useful in the diagnosis and follow-up of numerous airway diseases other than central neoplasms. Many research centers have been conducting tests to assess the applicability of pCLE in non-neoplastic diseases, which includes the diagnosis and reevaluation of patients with alveolar proteinosis, detecting filling of the alveolar space and the need for lung lavage[7]; the follow-up of lung transplant recipients, it being possible to detect early graft rejection[8]; the diagnosis of pneumonia, such as that induced by administration of amiodarone[9]; infection with *Pneumocystis jirovecii* in HIV-infected patients[10]; and even the diagnosis of pulmonary fibrosis.

Although pCLE is still in development, it is a method that is quite promising. Microscopic assessment of the airways and lung parenchyma without the need for tissue collection for histopathological examination is among the main advantages of pCLE, given that it reduces the risk inherent in any biopsy method, minimizing the risk of complications for patients requiring a diagnosis of lung diseases. However, further studies are needed in order to confirm the applicability and reproducibility of pCLE for clinical use instead of the methods currently in use, as well as to quantify the cost reduction resulting from its use.

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Evaluation of the gauge of needles used in the collection of specimens during endobronchial ultrasound-guided transbronchial needle aspiration

Goohyeon Hong[1,a], Ji Hae Koo[2,b]

TO THE EDITOR:

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a minimally invasive procedure that is widely used to sample mediastinal lesions, hilar lesions, and lesions adjacent to the central airway.[1,2] EBUS-TBNA was originally performed using dedicated 22-gauge needles. Recently, 21-gauge needles have been employed to improve the quality of biopsy specimens. The relative sampling utility of 21-gauge needles, in comparison with that of 22-gauge needles, remains controversial.

In the present study, we assessed the adequacy of histological specimens and the cellularity of cytological specimens obtained with 21- and 22-gauge needles. We analyzed data related to patients referred to a university hospital for EBUS-TBNA between 2014 and 2016. We included consecutive patients with hilar/mediastinal lymphadenopathy or tumors adjacent to the central airway. EBUS-TBNA was performed under local anesthesia with light conscious sedation with a convex-probe ultrasound bronchoscope (BF-UC260FW; Olympus, Tokyo, Japan) and a dedicated ultrasound scanner (EU-ME1; Olympus). All procedures were performed by the same pulmonologist. The needle gauge used was at the discretion of the operator, who employed either 21-gauge or 22-gauge dedicated needles (ViziShot, NA-201SX-4021 or NA-201SX-4022; Olympus). Only one sampling needle was used for each patient. Rapid on-site cytology evaluation was not performed.

The cytological and histological quality of needle aspirates was assessed by an experienced pathologist blinded to the needle gauge used. Each histological specimen was evaluated separately and categorized as follows: class I, diagnostic; class II, non-diagnostic but adequate; or class III, non-diagnostic and inadequate. In brief, specimens of classes I and II were considered adequate, either allowing a specific diagnosis to be made or at least containing elements indicating that the target lesion had been sampled. Cellularity was graded as follows: A, high (60–100%); B, moderate (30–59%); C, low (5–30%); D, scant (< 5%); or E, none (no lymphoid cells). Specimens of grades A, B, and C were considered adequate.

We evaluated 115 lesions from 68 cases (59 male patients and 9 female patients). The mean age of the patients was 63.5 years (range, 27-84 years). Based on the histological analysis, 57 patients had malignancies and 11 had benign lesions. A total of 57 lesions (in 36 patients) were punctured by 21-gauge needles, and 58 lesions (in 32 patients) were punctured by 22-gauge needles. The mean number of lesions punctured per patient was 1.69 (range, 1-3) and the mean total passes per patient was 4.20 (range, 2-9). The mean short axis diameter of the targeted lesions was 13.5 mm (range, 5-53). We found no significant between-group differences in terms of gender, age, prevalence of primary malignancy, lesion size, location, or number of needle passes.

Of the 57 lesions punctured by 21-gauge needles, 50.9% yielded class I specimens, 31.6% yielded class II specimens, and 17.5% yielded class III specimens. Of 58 lesions punctured by 22-gauge needles, 46.6% yielded class I specimens, 32.8% yielded class II specimens, and 20.6% yielded class III specimens. In the 21- and 22-gauge groups, adequate histological specimens were obtained in 82.5% and 79.4% of the procedures, respectively, a difference that was not significant ($p = 0.81$). Of the 57 specimens obtained with 21-gauge needles, 77.1% showed adequate cellularity and 22.9% did not, compared with 55.2% and 44.8%, respectively, of the 58 specimens obtained with 22-gauge needles. The cytological adequacy of the specimens obtained with 21-gauge needles was significantly higher than was that of those obtained with 22-gauge needles ($p = 0.018$). The histological classes, cytological grades, and qualities of the specimens are summarized in Table 1. We observed no major complications in either group.

In our study, 21-gauge needles were found to be superior to 22-gauge needles in terms of providing high-quality cytological specimens, although the adequacy of the histological specimens did not differ between the two groups. Six studies have assessed the effects of needle gauge in EBUS-TBNA,[3-8] although the results remain controversial. Saji et al.[3] reported that diagnostic accuracy was significantly higher when a 21-gauge needle was used than when a 22-gauge needle was used, and use of the former greatly improved the diagnosis of malignancy. Jeyabalan et al.[7] found that 21-gauge needles were superior to 22-gauge needles in terms of histopathological assessment of benign lesions (especially sarcoidosis) and malignant mediastinal lymphadenopathy. Nakajima et al.[5] reported that the number of cells in cytological specimens was significantly greater when 21-gauge needles were used than when

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Table 1. Classification of the specimens obtained by endobronchial ultrasound-guided transbronchial needle aspiration.[a]

Variable	EBUS-TBNA Needle size		p*
	21-gauge (N = 57)	22-gauge (N = 58)	
Histological specimen class			
I. Diagnostic	29 (50.9)	27 (46.6)	0.81†
II. Non-diagnostic but adequate	18 (31.6)	19 (32.8)	
III. Non-diagnostic and inadequate	10 (17.5)	12 (20.6)	
Cytological specimen grade[b]			
A. High	10 (17.5)	8 (13.8)	0.018‡
B. Moderate	24 (42.1)	13 (22.4)	
C. Low	10 (17.5)	11 (19.0)	
D. Scant	3 (5.4)	14 (24.1)	
E. None	10 (17.5)	12 (20.7)	

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration. [a]Data are presented as n (%). [b]A, high (60–100%); B, moderate (30–59%); C, low (5–30%); D, scant (< 5%); or E, none (no lymphoid cells). *Fisher's exact test. †Classes I and II vs. class III. ‡Grades A, B, and C vs. grades D and E.

22-gauge needles were used, and the extent of histological preservation was significantly greater when the former were used in order to sample malignant lesions. Oki et al.[4] reported that no difference in sampling yield between 21- and 22-gauge needles, both of which afforded good yields. Yarmus et al.[6] performed a retrospective multicenter (six-center) study and found that neither the diagnostic yield nor sample adequacy differed according to the gauge of needle used, although significantly fewer passes were required when 21-gauge needles were used than when 22-gauge needles were used, supporting the idea that the use of the former can increase the quantity of core tissue obtained and the extent of histological preservation. Most recently, Muthu et al.[8] assessed the diagnostic yield and adequacy (granuloma density) of histological specimens obtained with 21- and 22-gauge needles from patients with sarcoidosis. The authors found no difference between the two groups in terms of diagnostic yield or adequacy of the aspirate.

Theoretically, a larger-diameter (21-gauge) needle provides samples of higher volume.[9] However, we found no significant differences between 21- and 22-gauge EBUS-TBNA needles in terms of the diagnostic yield or adequacy of histological specimens, which is in keeping with the findings of previous studies.[4-6,8] That might be attributable to the inner diameters of both needles being sufficiently large to allow adequate histological sampling of core tissue.[10] In addition, because multiple lymph nodes are generally sampled in multiple passes, the amount of histological material obtained is usually diagnostically adequate. Although the adequacy of histological specimens obtained using either needle gauge has been debated, a trend toward improved sample adequacy when 21-gauge needles are used was apparent in our study. In particular, the quality of cytological specimens obtained with 21-gauge needles was significantly superior to that of those obtained with 22-gauge needles. Although gross and macroscopic specimen collection was easier when 21-gauge needles were employed, 22-gauge needles are especially suitable for EBUS-TBNA. Such needles have soft sheaths, which improves convex probe EBUS flexion even when the needle is inside the working channel. That facilitates EBUS-TBNA and allows acquisition of samples from nodes in the more distal parts of the airways.

In summary, we found no significant difference between 21- and 22-gauge EBUS-TBNA needles in terms of the adequacy of the histological specimens obtained. However, 21-gauge needles were superior in terms of providing adequate cytological specimens.

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Solitary fibrous tumor of the pleura: a rare cause of elevation of the right lung base

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DEAR EDITOR:

A 42-year-old female nonsmoker with no history of comorbidities was admitted to the hospital with a 6-month history of right-sided chest pain and dyspnea. A chest X-ray showed marked elevation of the right lung base (Figures 1A and 1B). Laboratory test results were unremarkable. A magnetic resonance imaging scan of the chest revealed a heterogeneous mass in the right hemithorax, with intermediate signal intensity on T1- and T2-weighted images (Figures 1C and 1D). A transthoracic needle biopsy was performed, and the results were inconclusive. The patient underwent radical surgical resection by open thoracotomy. The tumor was pedunculated, with free margins, measuring approximately 12 × 11 × 6 cm, and the pedicle was connected to the mediastinal pleura. The final diagnosis was solitary fibrous tumor of the pleura (SFTP). The postoperative evolution was uneventful.

Elevation of the right lung base may occur associated with elevation of the right hemidiaphragm or with the diaphragm in normal position. In the first condition, the main causes are phrenic paralysis[1] and the presence of an expansive lesion (e.g., a hepatic tumor or a subphrenic abscess) below the diaphragm. In the second condition, the main cause is infrapulmonary pleural effusion, although other, uncommon, causes include pleural tumors, such as SFTP.

A solitary fibrous tumor is defined as a mesenchymal neoplasm that has fibroblastic characteristics and clear peripheral vascular tumor-like branching vascularization. Although such tumors most commonly affect the pleura, they can occur in other thoracic areas (i.e., the mediastinum, pericardium, and lung), as well as in extrathoracic areas (i.e., the abdomen, head/neck, and central nervous system).[2-4]

An SFTP is often asymptomatic and discovered incidentally by radiography performed for other reasons. When signs and symptoms (including digital clubbing and hypertrophic osteoarthropathy) are present, they are usually associated with larger tumors. Patients with SFTP occasionally have hypoglycemia, which is seen more often in patients with malignant SFTP and is known as Doege-Potter syndrome. Doege-Potter syndrome is believed to be a type of non-insulin-dependent hypoglycemia.[2,3]

Computed tomography (CT) of a small SFTP frequently demonstrates a homogeneous, well-defined, noninvasive, lobular soft-tissue mass, usually adjacent to the chest wall or within a fissure. Larger lesions are typically heterogeneous and may not exhibit CT features suggestive of focal pleural tumors.[4] Heterogeneous areas of low attenuation on unenhanced CT scans may be caused by hemorrhage, necrosis, or cystic changes.[3,4] Changes in tumor location can be detected and are often related to the attachment of a benign SFTP to the pleural tissue through the pedicle.[3] Most localized fibrous tumors arise from the visceral pleura, and nearly half are pedunculated, the vascular supply to the tumor being contained within the pedicle.[4]

SFTPs show variable signal intensity on magnetic resonance imaging. The masses have predominantly low or intermediate signal intensity on T1- and T2-weighted images. They may also present high signal intensity on T2-weighted images. It has been suggested that this variable signal intensity is mainly dependent on the relative amounts of collagen and fibroblasts, as well as on the presence of areas of hemorrhage, necrosis, or cystic degeneration within the tumor. Intense heterogeneous enhancement after intravenous administration of gadolinium is typical and is generally due to high vascularity.

Making the differential diagnosis between benign and malignant SFTP is usually problematic. Although some imaging aspects, such as changes in the tumor location (suggesting the presence of a pedicle) and homogeneous attenuation of the lesion, are often associated with benign tumors, most authors have found that malignant lesions are indistinguishable from those with benign histological characteristics on imaging methods.[2,3-5] Currently, SFTP is primarily diagnosed on the basis of microscopic pathology findings, especially those obtained with immunohistochemical techniques.[2,4] On histological analysis, localized fibrous tumors appear as low-grade neoplasms with variable cellularity. The tumor cells are ovoid to spindle-shaped with round to oval nuclei, evenly distributed fine chromatin, inconspicuous nucleoli, and bipolar faintly eosinophilic cytoplasm with indistinct cell borders. Nuclear pleomorphism is minimal, and mitoses are usually rare or absent. Cellularity is variable and is inversely related to collagen content. Areas of necrosis, hemorrhage, or cystic degeneration may be evident, particularly in lesions that are large or in malignant lesions. Immunohistochemical staining shows that tumor cells are immunoreactive for CD34 and Bcl-2, albeit they typically lack expression for cytokeratin or S-100 protein.[2-4] Complete surgical excision is the treatment of choice and is the only effective treatment.

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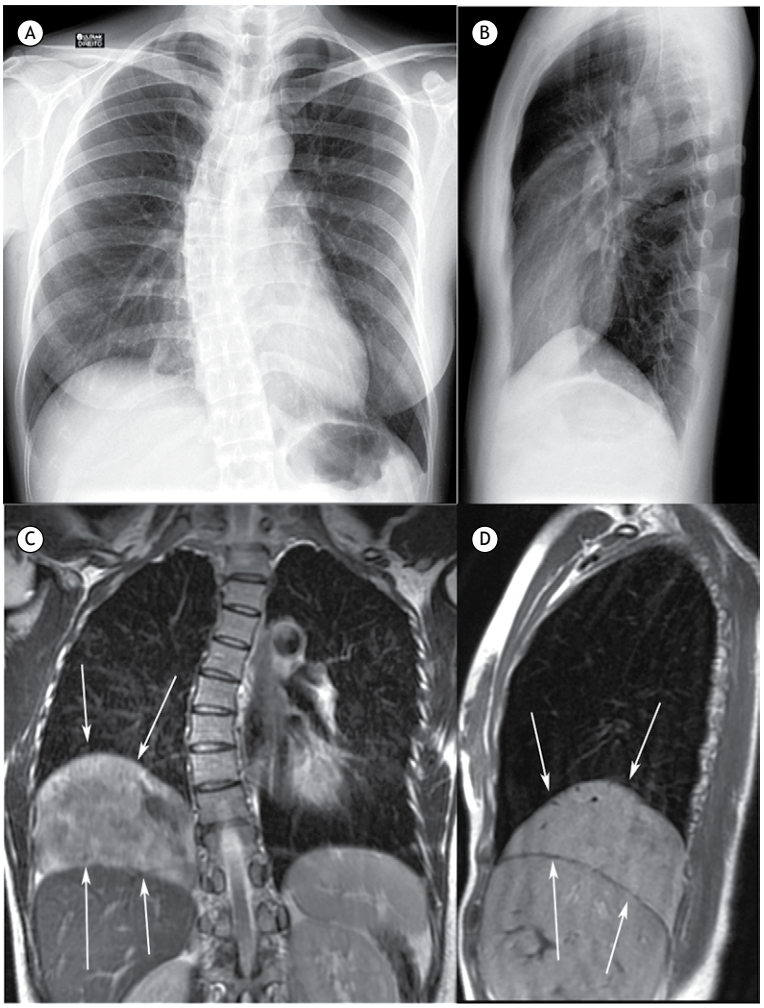

Figure 1. Frontal and lateral chest X-rays (A and B, respectively) showing elevation of the right lung base. Unenhanced coronal T2-weighted and sagittal T1-weighted magnetic resonance imaging scans (C and D, respectively) showing a large mass (arrows) occupying the inferior region of the right hemithorax with a heterogeneous, intermediate signal. The mass lies between the right lung base and the liver, with a well-defined cleavage plane between the two.

The prognosis for patients with SFTP is generally favorable. However, in a small number of cases, the lesions recur, undergo malignant transformation, or metastasize.[2,3]

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Use of thrombolytic agents in the treatment of acute pulmonary thromboembolism: things are not as simple as you might think

Carlos Henrique Miranda[1,a]

I congratulate Fernandes et al. on their review article entitled "Reperfusion in Acute Pulmonary Thromboembolism" (PTE) published in the JBP.[1]

I would like to make some practical comments on and comparisons with the use of thrombolytic agents in acute myocardial infarction (MI), initially with regard to high-risk group patients who present with hemodynamic instability—systolic blood pressure (SBP) < 90 mmHg or a sustained ≥ 40-mmHg decrease in SBP for 15 minutes in the absence of other reasons, such as new-onset arrhythmias, hypovolemia, or sepsis.[2] The use of thrombolytic agents in high-risk group patients has been reported to reduce the relative risk of death by 80%; however, according to one study, up to two thirds of such patients do not receive fibrinolytic agents.[3] This reduction in the relative risk of death is substantially larger than that observed in acute ST-segment elevation MI (STEMI), with ranges from 20-30%, according to one study.[4] Nevertheless, thrombolytic agents are widely used in acute STEMI, and not prescribing fibrinolytic therapy, especially when primary angioplasty is unavailable, is considered poor medical practice. I believe that the use of thrombolysis in high-risk PTE should be encouraged, provided that absolute contraindications are taken into account. Recently, a directive published in the Brazilian Official Federal Government Journal[5] mandated that the indication for alteplase in treating PTE be incorporated into the Brazilian Unified Health Care System. We should also be alert to the fact that several patients have borderline SBP (90-110 mmHg), and sometimes it is difficult to establish baseline blood pressure levels in order to determine whether there is a ≥ 40-mmHg decrease. In such cases, I recommend measuring serum lactate levels. Serum lactate levels > 2.0 mg/dL suggest that the observed blood pressure level is not adequate for tissue perfusion. If that is the case, the patient also meets the criteria for circulatory shock, since lactate levels are essential to detecting hemodynamic collapse. Some investigations have shown that lactate in this context is an independent predictor of mortality, being a better prognosticator than either troponin or N-terminal prohormone of brain natriuretic peptide (NT-proBNP).[6,7] Such a patient also meets criteria for thrombolysis.

With regard to the use of thrombolytic agents in intermediate-risk patients, I believe that the controversy continues, because a single randomized study does not provide enough evidence for a final verdict. We should consider that the markers used have a low positive predictive value for identifying patients at high risk for complications. Optimal cut-off values for troponin and NT-proBNP have not yet been established and may vary according to the method used for determining their levels. With regard to echocardiography, there is no methodological standardization for evaluating the right ventricle. Therefore, I consider it a great challenge to establish new parameters with adequate accuracy for selecting patients who are truly at risk, and perhaps these are the patients who can benefit from fibrinolytic therapy.

One study[8] that investigated thrombolysis with tenecteplase in intermediate-risk patients had numerous setbacks. First, the thrombolytic agent chosen. In this setting, the largest experience has been with alteplase. Tenecteplase's ease of administration as an i.v. bolus is a plus; however, the disadvantage is its duration of action (40 min), whereas alteplase's duration of action is 2 hours, which guarantees longer exposure time for thrombus dissolution, especially in patients with high thrombotic load. In a meta-analysis of the use of thrombolytic agents in PTE, alteplase did not increase the risk of bleeding (OR = 1.07; 95% CI: 0.43-2.62); however, this risk increased considerably with the use of tenecteplase (OR = 5.02; 95% CI: 2.72-9.26).[9] Therefore, I believe that alteplase should be considered the first choice for reperfusion in PTE. Second, the study by Meyer et al.[8] did not adjust the dose of tenecteplase for elderly patients, and although the use of tenecteplase was found to reduce the composite outcome of mortality and hemodynamic decompensation from 5.6% to 2.6% (p = 0.02), it caused a higher number of intracranial bleeds (2.0% vs. 0.2%; p = 0.003). In that study,[8] subgroup analysis demonstrated that the clinical benefit was limited to patients ≤ 75 years of age (OR = 0.33; 95% CI: 0.13-0.85). Of the 11 patients who had intracranial hemorrhage, 9 (82%) were ≥ 75 years of age.[8] Armstrong et al.[10] addressed thrombolysis with tenecteplase followed by angiography in the treatment of acute STEMI, initially demonstrating an increase in the rates of intracranial bleeding in patients ≥ 75 years of age who received tenecteplase (1.0% vs. 0.2%; p = 0.04); after an amendment to the study protocol, with the dose of tenecteplase being reduced by half in patients ≥ 75 years of age, the bleeding rate was equivalent between groups (0.5% vs. 0.3%; p = 0.45). Third, the recommended dose of unfractionated heparin for use with the thrombolytic agent in PTE is an i.v. bolus of 80 IU/kg, followed by 18 IU/kg per hour continuous infusion, with adjustment of the activated partial thromboplastin time (aPTT) to 2.0-2.5 × normal. One study on the use of fibrinolytic agents in acute STEMI showed a reduction in bleeding with the use of a lower-dose heparin regimen

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(60 IU/kg bolus; maximum, 4000 IU; followed by 12 IU/kg per hour continuous infusion; maximum, 1000 IU/h) with a target aPTT between 1.5 and 2.5.[11] After thrombolysis for PTE, it is not uncommon that patients are started on heparin therapy and that the first aPTTs reveal non-coagulability of blood, precisely at this stage when the risk of bleeding is more critical. In the study by Meyer et al.,[8] 30% of the patients had heparin levels above recommended levels. Why not start infusion more cautiously and gradually adjust it upward if necessary? And, finally, that study reported low mortality (2.4% in the tenecteplase group vs. 3.2% in the control group), which may be due to early diagnosis and treatment in European centers, from where the patients were recruited.[8] However, a sample of patients in Brazil had a higher mortality rate of approximately 20%, which may be due to delayed diagnosis because of difficulties within the Brazilian Unified Health Care System.[12] In this context, the role of fibrinolytic agents may be more prominent.

PTE is a neglected health problem, especially when compared with acute STEMI. With regard to treatment of low-risk patients, the institution of heparin therapy is sufficient. For high-risk group patients, we need to promote the use of thrombolysis. And, regarding intermediate-risk group patients, we still need to improve our scientific basis before establishing definitive approaches.

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Authors' reply

Reflections on the use of thrombolytic agents in acute pulmonary embolism

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The use of systemic thrombolytic agents for the treatment of acute pulmonary embolism is a controversial subject, in which evidence and belief eventually clash. While there is no dispute regarding the benefits of the procedure for high-risk patients,[1] this indication is much more debatable for intermediate-high-risk patients. These latter patients are characterized by maintaining adequate levels of tissue perfusion at the expense of right ventricle injury. It is quite tempting to imagine that pharmacological intervention at this point would prevent progression to right ventricular failure, cardiovascular collapse, and death. It is also intuitive to seek a long-term benefit from the use of thrombolysis in intermediate-high-risk patients; after all, by reducing the thrombotic load, it would be possible to reduce any residual vascular obstruction, thereby reducing the risk of chronic thromboembolic pulmonary hypertension. However, thrombolysis indisputably increases the risk of bleeding. So what to do? The physiological rationale is not always the best path to take. In such cases, seeking the best evidence available can provide better answers.

The study by Meyer et al.[2] is the largest and best study to date to evaluate thrombolysis versus heparin therapy in intermediate-risk patients systematically, although it is not the only one.[1] The number of patients evaluated in the study by Meyer et al.[2] is larger than the total number of patients in all studies that investigated alteplase, the most traditionally used drug in such cases (1006 vs. 657). This results in tenecteplase being the most commonly investigated thrombolytic agent in phase III trials in pulmonary embolism today. In addition, because of the large number of patients, the study by Meyer et al.[2] has an 80% power of detection of intergroup differences. All those studies, with the one by Meyer et al.[2] being the most representative, tend to converge on the same finding: while the use of thrombolytic agents poses an increased risk of bleeding, which is greater in the population known to be at risk, such as the elderly, the benefits of thrombolysis, whether with alteplase, tenecteplase, urokinase, or streptokinase, appear to be quite modest. Traditional heparin therapy appears to be quite safe, with a mortality rate of 1.8% if good medical practices are followed. Monitoring of intermediate-high-risk intensive care patients and prompt institution of reperfusion at the first sign of hemodynamic instability are mandatory prerequisites. However, if these prerequisites are met, and with such low mortality rates, is it worth performing thrombolysis, since conventional therapy is effective? The most reasonable solution appears to be conventional therapy, intensive monitoring, and early reperfusion if there is any sign of hemodynamic instability. And, as suggested earlier, it is possible that lactate levels play a role in this monitoring.

Long-term benefits also do not justify the use of thrombolysis. Data from a study by Konstantinides et al.[3] identified no benefits in mortality rates, residual dyspnea, or diagnosis of chronic thromboembolic pulmonary hypertension. If the short-term benefit is small, the medium-term benefit is zero, and there is the risk of further morbidity, such as bleeding, why do it indiscriminately? Of course, if the choice if for thrombolysis, hemorrhage should be prevented by dose adjustment for weight and age, pressure control, and use of a proton pump inhibitor. Even so, does the benefit justify the risk? To date, the best available evidence tells us that it does not.

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1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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XXI Congresso da Sociedade
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ERS 2019
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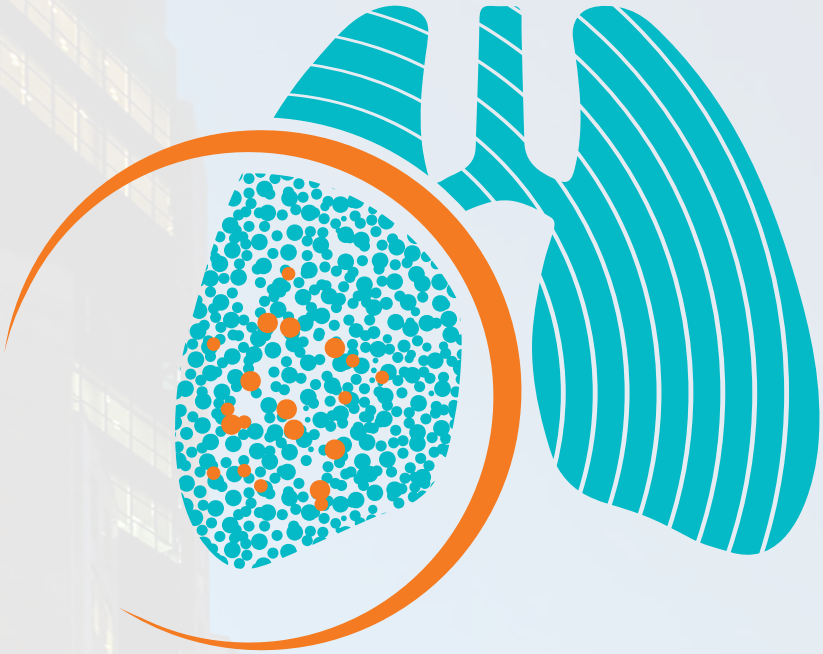

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