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HIGHLIGHT

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Robotic thoracic surgery: initial experience in Brazil

Characterization of lung cancer in Brazil

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Revisiting 2019, setting goals for 2020, and reflecting upon open science

Bruno Guedes Baldi[1,2]

The major objectives of the *Jornal Brasileiro de Pneumologia* (JBP, Brazilian Journal of Pulmonology) are to disseminate Brazilian research in the field of respiratory diseases and related areas, to expand the internationalization of the journal, and to act as one of the major sources of updates for the members of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society), increasingly reaching out to our readers. The JBP will celebrate its 45th anniversary in 2020. Since its inception, it has matured in the dissemination of knowledge by monitoring the developments and occasional events occurring in the field of pulmonology, continuing to be the leading Latin American journal in the field. The secondary and indirect objectives that should be highlighted are to increase the interest of recent graduates in the field and to promote the development of new researchers in related areas.

In 2019, various goals proposed by the current board of the JBP were achieved. Of those, we would like to highlight the following[1]:

- Adoption of the continuous publication model, maintaining the number of six issues per year, in order to reduce the time between approval and online availability of the articles, followed by discontinuation of publication of the printed version
- Increasing the number of editorials with the participation of international authors, thus enhancing the visibility of the journal
- Continuation of the process of updating guidelines and consensuses on major respiratory diseases, which constitute an important instrument for consultation and assistance in addressing such diseases, especially for pulmonologists in Brazil[2,3]
- Broader dissemination of select articles on social networks, such as Twitter, Facebook, and Instagram, including comments by the authors
- Updating the instructions to authors and reviewers
- Systematic use of the iThenticate tool to check for plagiarism in all articles to be reviewed
- Creation of the Continuing Education in Respiratory Physiology section, which has been well evaluated in a recent poll (data not shown)
- Strengthening the partnership with the Pulmonology Journal (formerly the *Revista Portuguesa de Pneumologia*) to expand the dissemination of the JBP and its articles
- Publication of thematic issues on tuberculosis and COPD

There are various goals for the JBP in 2020, the year of its 45th anniversary:

- Increasing the impact factor—to be updated in 2020—which is based on the number of articles cited to date
- Management of the Digital Object Identifier (DOI) directly by the JBP, dispensing with the need for intermediation by SciELO, in order to streamline the registration of the articles in the CrossRef database
- Updating the JBP website to improve the layout, increase the speed of access, and expand the number of tools available
- Inclusion of links to podcasts on top articles
- Optimization of the time from approval to the online publication of articles, thus increasing their dissemination and the number of potential citations
- Initiating the publication of guidelines on the pharmacological treatment of respiratory diseases based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,[4] which will inform decisions regarding the definition of public policies
- Increasing the number of review articles that facilitate daily practice in the field of respiratory diseases, including topics of greater interest to the JBP readers.

In Plan S,[5] organized by an international coalition, as well as in presentations in various forums and publications by the SciELO Program, it has been suggested that open practices of scientific communication be adopted over the next five years. This scientific model includes open and unrestricted access to all peer-reviewed publications, acceptance of manuscripts previously deposited on a preprint server, adoption of the continuous publication modality, making all research content available in detail, and the possibility of open peer review.[5-8] However, although most of the proposals put forth have been in agreement regarding open communication, which will certainly contribute to the progress of science, establish greater transparency in editorial processes, and democratize access to information, there are still certain questions about the universal adoption of this policy, even within the international scientific community, especially regarding the possibility of opening the peer review process (i.e., disclosing the identity of the reviewers to the authors). Certainly, there are advantages to an open peer review process, because it will increase the importance of the reviewers and promote a trend toward improvement of the quality of the evaluations, because all of the participants are likely to be more careful in carrying out their part in the process and to venture out of their comfort zone. However, there are potential negative aspects of this process, including a higher risk that reviewers will decline to participate in the peer review process (given that it has already been difficult to find reviewers in the various areas of knowledge using the traditional model) and a potential risk of "retaliation" by

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authors in the event of negative reviews regarding the manuscript in question.

We should recognize that there is still much room for improvement and that the task is not a simple one. However, I would like to emphasize the key roles played by the editors, reviewers, editorial assistants, and board of directors of the Brazilian Thoracic Society, as well as by the authors and the readers, in improving and increasing the international recognition of the JBP, so that the JBP becomes a target journal even for authors in other countries due to the improvement of the quality of the articles. There are various ongoing challenges, including the need to expand the number of reviewers and the number of international collaborations in the articles published, as well as to promote partnerships among Brazilian research groups. In addition, we should seek to shorten the turnaround time for the initial peer review and streamline the online publication process in order to help improve the quality of the submissions received and provide information to the readers in a more reliable manner. We also need to broaden the discussion in order to consolidate the universal adoption of open science communication practices in the coming years, as advocated in Plan S and the SciELO Program.[5-8] We welcome critiques and suggestions for the improvement of JBP.

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Lung cancer staging in Brazil: an epidemiological perspective

Juliana Pereira Franceschini[1], Ilka Lopes Santoro[1]

In terms of incidence and mortality rates, lung cancer is the leading type of cancer worldwide.[1] Smoking is the main preventable risk factor for the development of lung cancer.[2]

Brazil is notable for its anti-smoking measures, which have contributed to a decrease in the prevalence of smoking among Brazilians in recent decades. However, despite efforts to control tobacco use in the country, lung cancer has a long latency period, which affects the associated incidence and mortality rates.[3] Malta et al.[4] demonstrated a slight decrease in the lung cancer mortality rate among men in Brazil between 1996 and 2011, no such decrease having yet been observed among women in the country.

In a retrospective epidemiological study published in this issue of the JBP, Costa et al.[5] profiled 73,167 patients diagnosed with lung cancer in Brazil between 2000 and 2014, stratified by the stage of the disease. Their study is extremely important and yielded relevant results, the analysis of which will facilitate the rethinking of national health care policies related to lung cancer.

Costa et al.[5] obtained data from the Hospital Cancer Registry System of the Brazilian National Cancer Institute, located in the city of Rio de Janeiro, Brazil, and from hospital cancer records of the Cancer Center Foundation of São Paulo, in the city of São Paulo, Brazil. Because their analysis was retrospective and based on data from tertiary cancer hospitals in large Brazilian capitals, it is necessary to consider the biases inherent to the study design. First, there are difficulties in generalizing the results, which may not reflect the vastness of the country and the consequent differences in geography, culture, and access to health care services. Similarly, Kaliks et al.[6] demonstrated significant differences in the systemic treatment of cancer in Brazil, in terms of the medications available as well as in terms of the treatment protocols, attributing those differences to the lack of broad discussions, among governmental entities, the medical community, and civil society, on the topic.

It should be borne in mind that, during the period evaluated by Costa et al.[5], new technologies for the diagnosis and treatment of lung cancer were incorporated into daily practice. Notable among such technologies is positron-emission tomography/CT, which was incorporated into the clinical routine at the National Cancer Institute in 2013, although it had been used in clinical trials since 2010. This method contributes to the refinement of the clinical staging of cancer and might therefore have, in part, influenced (and could explain) the distribution curves of the disease stages, especially since 2010.

Costa et al.[5] found that, in Brazil, as in most countries, lung cancer is diagnosed at advanced stages of the disease (stages III and IV) in approximately 70% of cases. Delayed diagnosis of lung cancer is associated with low survival rates, greater impairment of quality of life, and higher treatment-related costs.[7]

Another aspect to be highlighted is that, during the Costa et al.[5] study period, the tumor-node-metastasis staging system for lung cancer was updated twice (from the 5th to the 6th edition and from the 6th to the 7th edition).[8] Therefore, major changes in the descriptors should be taken into consideration, especially regarding the tumor and metastasis components and, consequently, the clinical staging over time, because there is no homogeneity in the definition of intra-stage descriptors.

Over the course of the study period, Costa et al.[5] demonstrated an increase in the prevalence of adenocarcinoma and a reduction in the prevalence of squamous cell carcinoma. That is in accordance with the findings of other studies in the literature.[9,10]

We emphasize the merit of having a national cancer registry database to encourage population-based studies on the subject, which are of paramount importance to establish public policies related to the management of lung at step of the process, from diagnosis to treatment. We agree with the authors that the training of professionals working at the primary and secondary health care levels is crucial, as is the coordination of health care services, in order to create a linear system of care that optimizes the use of time and resources for the early diagnosis of lung cancer, with the objective of providing treatment aimed at achieving a cure.

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Directions for robotic surgery in the treatment of thoracic diseases in Brazil

Jefferson Luiz Gross[1]

A minimally invasive surgical approach is the recommended option for the treatment of lung cancer, especially in the early stages.[1] The first form of minimally invasive surgery was video-assisted surgery, which began to be employed in the treatment of thoracic diseases in the early 1990s. In the last decade, robotic surgery has emerged as another minimally invasive surgical option. In comparison with video-assisted surgery, the use of robotic thoracic surgery has been growing faster, especially in more developed countries.[2] Although the first reports of the use of robotic surgery in the treatment of thoracic diseases in Brazil were published in 2011, the feasibility of the robotic approach in the surgical treatment of patients with lung cancer was not demonstrated until 2016, when Terra et al.[3] reported their initial experience with the technique. Although not yet widespread, the use of robotic thoracic surgery has been growing in Brazil. In the field of thoracic surgery, the main applications of robotic surgery are in the treatment of lung cancer and mediastinal tumors. This issue of the JBP includes the largest studies to date presenting the Brazilian experience with robotic surgery in the treatment of tumors of the thymus[4] and lung cancer.[5]

Terra et al.[4] report their initial experience in a sample of 18 patients with tumors of the thymus who underwent robotic surgery at a total of seven centers in Brazil. The authors reported technical aspects and results, such as operative time, extent of resection, length of hospital stay, and postoperative complications. There were no intraoperative accidents, and no cases were converted to video-assisted or open surgery. The most relevant results were the median drainage time and median length of hospital stay (only 1 and 2 days, respectively). There were no postoperative deaths, and only 3 cases presented complications (elevation of the hemidiaphragm, in 2, and chylothorax, in 1). Of the 18 patients, only 1 had positive surgical margins, receiving adjuvant chemotherapy and radiotherapy after surgery. The follow-up period was too short to provide estimates on cancer outcomes. With this report of their initial experience,[4] in the form of a case series, the authors demonstrated that robotic thoracic surgery for the treatment of thymic tumors is feasible and safe for use in Brazil.

The most common application of robotic surgery in thoracic diseases is in the treatment of lung cancer, due to the high incidence of the disease. In another article published in this issue of the JBP, Terra et al.[5] report the 40-month experience of six Brazilian institutions, with a collective total of 154 patients, using robotic surgery for the resection of lung cancer. The morbidity rate was 20.4%, and the mortality rate was 0.5%. From an oncological point of view, the surgical resection was categorized as complete in 97.4% of the cases and as uncertain, due to the involvement of mediastinal lymph nodes, in only 2.6%. Although the follow-up period was short (mean, 326 days), the overall survival rate during follow-up was 97.5%. These results demonstrate that, in Brazil, robotic surgery for the treatment of lung cancer patients can be performed properly and safely, which consolidates its status as an acceptable option for minimally invasive surgery.

Although the studies detailed above describe initial experiences in Brazil,[4,5] the morbidity and mortality rates reported are very similar to those reported in various international studies,[6] demonstrating that robotic surgery results in pleural drainage times and hospital stays are shorter than those reported for other techniques.[7] Oh et al.[8] published results from a study of patients who underwent lobectomy in the USA. The authors compared three techniques: robotic surgery, video-assisted surgery, and thoracotomy. In comparison with thoracotomy, robotic surgery was found to result in lower postoperative complication rates, shorter hospital stays, and lower postoperative mortality.[8] In addition, the results suggest that robotic thoracic surgery maintains the basic principles of surgical resection of cancer. We must bear in mind that, despite its novelty, the robotic technique should never be allowed to change the principles of the surgical treatment of cancer. Studies with longer follow-up periods have reported oncological results similar to those obtained with thoracotomy and video-assisted surgery.[9] Kneuertz et al.[10] suggested that the robotic technique is more well suited to mediastinal lymphadenectomy than is the video-assisted technique, which gives the former a great oncological advantage.

Technological advances, together with the increasing experience of surgeons, have expanded the indications for robotic thoracic surgery.[11] Even in Brazil, the use of robotic thoracic surgery has been growing rapidly and in an organized manner. Training and certification processes play a key role in the safe and effective dissemination of the robotic technique. Although initial results from the Brazilian experience indicate that we are on the right track, some obstacles need to be overcome. The high cost of incorporating new technologies is always a big issue. However, with the improvement of training, education, and standardization of procedures, the results look quite promising. Kneuertz et al.[12] demonstrated that, for lung cancer resection, robotic surgery is more cost-effective than is thoracotomy. The greater number of centers in different regions in Brazil is also an important step for increasing the access to and democratization of the

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technique, not only for surgeons who are interested in applying the technique but also for the patients who can benefit from its use.

The outlook for robotic thoracic surgery in Brazil seems to be positive, provided that careful training, qualification, and standardization of procedures are maintained. With these precautions, the safety and effectiveness of robotic surgery will be enhanced, contributing to improved cost-effectiveness and democratization of access to these technological advances.

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Upper limbs: how physically limited is your patient?

Karina Couto Furlanetto[1,2], Natielly Soares Correia[1], Simone Dal Corso[2]

Reference values for field tests to be used in clinical trials are obtained from a set of apparently healthy individuals, providing clinicians with a comparative basis for the correct interpretation of the results presented by the patient under evaluation.[1] In addition, by taking the reference values for such tests into account, it is possible to quantify objectively how limited the individual is. It is essential that normative values be established in a specific population, because various factors, such as demographic, anthropometric, clinical, and physiological factors, can influence test performance.[2]

There are a significant number of normative values for field tests, especially those involving the lower limbs, some for use in Brazil.[2] Based on those values, it is known that individuals with chronic diseases perform more poorly on those tests than do their healthy peers. However, normative values are scarce in the scientific literature regarding upper limb exercise tests, although we know that the use of the upper limbs in chronic lung disease triggers a series of changes in ventilation[3] and that the perceived level of exertion is similar to that related to the use of the lower limbs.[4] In addition, whereas the lower limb muscles are mostly responsible for limiting activities such as walking, it is known that approximately 80% of activities of daily living (ADLs) are performed with the upper limbs and that individuals with COPD commonly report dyspnea and fatigue during such activities.[4] When arm activities are unsupported, there is a reduction in inspiratory capacity and thoracoabdominal asynchrony, consequently increasing ventilatory demand and oxygen uptake, thus worsening dyspnea.[5-8] Although oxidative capacity is preserved and even increased in the deltoid muscles, which support the upper limbs, exercise tolerance is lower during activities performed with no upper limb support.[5] Therefore, the use of specific tests for upper limb assessment is crucial in patients who report some type of limitation in the performance of ADLs involving the upper limbs.

The Unsupported Upper Limb EXercise (UULEX) test is one of the recommended tests to assess upper limb functional capacity and endurance.[6] However, due to the lack of normative values for the Brazilian population, there is a gap in the literature regarding the correct interpretation of this test. In the current issue of the JBP, Lima et al.[7] have determined, for the first time, reference values for the UULEX test in healthy adults in Brazil. Their study involved a sample of 100 healthy Brazilian individuals over 30 years of age. The mean test completion time, the main outcome of the UULEX test, was 11.99 ± 1.90 min among the women and 12.89 ± 2.15 min among the men ($p = 0.03$). The regression model developed by the authors demonstrated that UULEX completion time was partly explained by the gender, age, and body mass index of the individuals, those variables collectively accounting for 30% of the variability in completion time.[7] Although the sample size was small and the adjusted coefficient of determination was low ($r^2 = 0.30$), a descriptive analysis of the performance of the individuals in the sample was carried out, providing normative values for men and women in each decade of life. In fact, those results will be very useful to assist in the interpretation of the UULEX test in young adults and elderly individuals in Brazil.

The following is a practical example of how to identify upper limb exercise limitation objectively in a population known to present with pulmonary and systemic impairment. Considering the new UULEX test normative values[7], we will interpret the performance of COPD patients in the study that introduced the UULEX test.[8] In that study, 9 patients underwent the test. The mean age of those patients was 62 years, and most were male. Therefore, we used the normative values obtained in the study conducted by Lima et al.[7] for males in the 61- to 70-year age group; that is, a mean UULEX completion time of 13.05 min (95% CI: 9.00-15.00). Thus, using a simple rule of three, we determined that the patients with COPD in that study showed 61% of the predicted values. Another example can be found in the study conducted by Janaudis-Ferreira et al.,[9] whose sample characteristics also lead us to consider the normative values for males in the 61- to 70-year age group. In that case, the UULEX completion time was 47% of the predicted value.[10] We find it interesting that the UULEX test has recently been validated for patients with rheumatoid arthritis.[11] The mean UULEX completion time was 8.26 min (95% CI: 2.30-11.00), which is below the normative value of 12.50 min (95% CI: 9.48-15.00) for women in the 51- to 60-year age group,[7] corresponding to 66% of the predicted value. Although these are only illustrative examples, because the samples of patients were in countries not included in the development of the normative values, this analysis is a way of showing their applicability not only in research but also in clinical practice.

Finally, the correct assessment of upper limb and lower limb functionality is fundamental for the practice of health care professionals, given that chronic diseases have a major impact on the ADLs of the patients.[12] We suggest that functional tests be administered by professionals

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who work directly with patients who report limitations in ADLs, whether related to the upper limbs, lower limbs, or both. Various tests have been developed for functional assessment and can be easily performed in physician offices, clinics, hospitals, and even in the home environment. It is up to us, health care professionals, to implement such tests and use normative values in clinical practice, so that the objective interpretation of the functional performance of the patients can facilitate clinical decision making.

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What does the increasing prevalence of obesity mean for the management of asthma and airways disease?

Jodie L Simpson[1], Hayley A Scott[1]

There is a global epidemic of obesity and, coinciding with this, a high prevalence of obesity coexisting with asthma. Research suggests that adults with asthma and obesity have asthma that is more severe, including poorer control, reduced lung function, and more frequent exacerbations, than do those with asthma who are not obese.[1] They also have a diminished response to asthma pharmacotherapy, including β_2 agonists, inhaled corticosteroids, and montelukast.[2] The reduced efficacy of maintenance and reliever medications likely plays an important role in poorer asthma outcomes. However, we still do not properly understand the impact that obesity has on asthma outcomes, the mechanisms responsible, or the ideal management approach, which represents a major problem.

In a study published in this issue of the JBP, Souza et al.[3] examined the prevalence of respiratory symptoms and asthma according to body mass index, as well as evaluating the factors associated with asthma in more than 1,000 adults 40 years of age or older. Their study was a cross-sectional subanalysis of the *Respira Floripa* study, in which the study population was derived from a metropolitan area in Brazil. Participants self-reported respiratory symptoms and underwent pulmonary function tests. The authors demonstrated that a diagnosis of asthma is more common in obese individuals, physician-diagnosed asthma being three times more common in individuals who are obese than in those of normal weight. This is in line with the findings of a 2007 meta-analysis showing that obesity precedes the development of asthma, nearly doubling the odds of incident asthma. In their study, Souza et al.[3] also showed that the prevalence of respiratory symptoms, particularly dyspnea and wheezing, are highest in obese individuals, irrespective of smoking status. Notably, the authors found that, among nonsmokers, chronic expectoration and chronic bronchitis-like symptoms were most common in those who were obese, whereas the prevalence of chronic expectoration did not differ by weight category among current and former smokers. That finding suggests that smoking masks the obesity-induced effects of mucous production. Among the nonsmokers, rhinitis was common and its prevalence was higher in those who were obese, whereas it was similar among the current and former smokers, independent of body mass index. This was an important real-world study that adds to our understanding of the impact of obesity in adults with asthma.

Although the mechanisms responsible for the association between obesity and asthma are not clear, it is likely due to a combination of inflammatory and mechanical influences. The rise in obesity is thought to be the result of changing lifestyles, a poor diet and physical inactivity being the key drivers. Such changes lead to excess adipose tissue, together with alterations in the microbiota and immune system, including increases in IL-6 and TNF-α.[4] Obesity is characterized by an increase in neutrophils, in the adipose tissue and in the circulation.[5,6] Our group,[4] as well as others,[7-9] observed an increase in neutrophils in the sputum of obese adults with asthma, suggesting that the systemic inflammatory effects of obesity extend to the airways of susceptible individuals with asthma. In relation to the mechanical effects, fat tissue in the chest wall reduces chest wall movement and chest cavity volume, whereas abdominal fat tissue limits lung inflation by reducing the ability of the diaphragm to shift downwards.[10] That may contribute to reduced lung function and the sensation of dyspnea in obese adults with asthma.

The effective management of asthma in obese individuals requires an individualized, multidisciplinary approach, including the assessment and treatment of comorbid disease. Souza et al.[3] found that wheezing and dyspnea were both more common in obese individuals. In another study conducted by our group,[11] we demonstrated that a 5-10% weight loss is effective for improving asthma control (including symptoms of wheezing and dyspnea), as well as lung function and asthma-related quality of life, in overweight and obese adults with asthma. Taken together, these findings suggest that, although obesity worsens wheezing and dyspnea, a modest weight loss can effectively reduce those symptoms. Souza et al.[3] also found that the prevalence of heart disease and diabetes is higher in obese individuals, who also have the highest incidence of asthma. This is indicative of the increasing burden of chronic disease in the population over 40 years of age and, because heart disease and diabetes are both also associated with increased systemic inflammation, underscores the need to assess and manage systemic and airway inflammation in individuals with asthma. The greater neck circumference in obese individuals also suggests that assessment and management of sleep apnea are likely to be critical and may improve quality of life in those with asthma. Although there have been some studies suggesting possible treatment pathways, much more research is needed. Due to the paucity of research in the area, guidelines for the management of obesity-associated asthma do not exist. Further studies such as this are urgently needed so that management guidelines can be developed.

In conclusion, the Souza et al. study[3] provides important new data regarding the association between obesity and a diagnosis of asthma, as well as the clinical consequences

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of obesity in individuals with established disease. The findings corroborate those of previous studies in this area and will facilitate the development of clinical guidelines for the management of obesity-associated asthma, which currently do not exist. Further research is needed in order to determine the ideal treatment pathway for managing symptoms and improving patient outcomes in obesity-associated asthma.

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Peripheral consolidation/ground-glass opacities

Edson Marchiori[1], Bruno Hochhegger[2], Gláucia Zanetti[1]

A 27-year-old HIV-positive male-to-female transsexual patient presented with a two-day history of progressive dyspnea. A CT scan of the chest showed diffuse ground-glass opacities predominantly located in the lung periphery (Figure 1).

Although any condition causing airspace filling can result in peripheral consolidation/ground-glass opacities, diseases in which consolidation/ground-glass opacities are predominantly located in the lung periphery include influenza A (H1N1) pneumonia, eosinophilic pneumonia, organizing pneumonia, fat embolism syndrome, and silicone embolism syndrome. Given that in many cases CT findings overlap among different diseases, correlation with clinical and laboratory findings will help narrow the differential diagnosis.

Common clinical findings in influenza A (H1N1) pneumonia include fever, cough, dyspnea, myalgia, headache, and hypotension. Although most patients present with mild symptoms, a small proportion of patients present with severe symptoms. Common laboratory abnormalities include lymphopenia, thrombocytopenia, elevated serum lactate dehydrogenase levels, elevated C-reactive protein levels, and elevated serum creatine kinase levels.[1]

The signs and symptoms of eosinophilic pneumonia are nonspecific and include dry cough, dyspnea, and, less frequently, malaise, myalgia, night sweats, chills, and pleuritic chest pain. The diagnosis of eosinophilic pneumonia is based on the presence of peripheral or BAL fluid eosinophilia and the exclusion of other diseases that can present with pulmonary infiltrates and eosinophilia.[2]

The diagnosis of organizing pneumonia is challenging because clinical, radiological, and laboratory findings are nonspecific. Organizing pneumonia can be idiopathic or secondary to infectious causes, iatrogenic causes (including medication and radiation therapy), and autoimmune diseases, among others. A definitive diagnosis of organizing pneumonia is based on histopathological evidence.[3]

Fat embolism refers to fat emboli in the pulmonary arteries (typically from bone marrow) after long bone fractures, orthopedic surgery, or cosmetic surgery (liposuction). Findings suggestive of fat embolism syndrome include respiratory symptoms, confusion, and petechiae in the conjunctiva, neck, or chest. Clinical and radiological manifestations typically occur within 24-48 h after the causative procedure.[4]

Our patient had received a liquid silicone injection into the buttocks one day before the onset of symptoms. A BAL revealed pulmonary hemorrhage and macrophages containing silicone vacuoles, thus confirming the diagnosis of silicone pulmonary embolism. Silicone pulmonary embolism is a relatively rare and potentially fatal condition that is largely due to subcutaneous injection of liquid silicone for cosmetic purposes.[5] Clinical, pathophysiological, and imaging findings are similar between fat embolism syndrome and silicone pulmonary embolism. The latter is most common in male-to-female transsexuals who inject silicone in order to feminize their bodies.

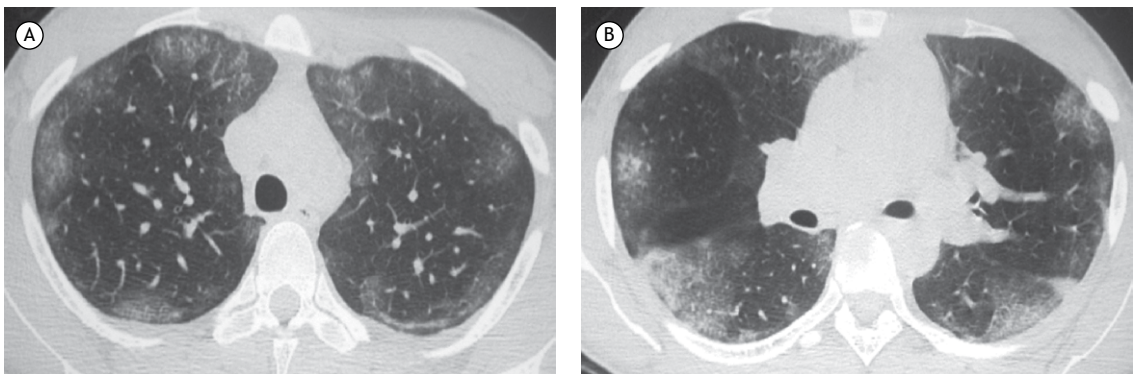

Figure 1. Axial CT scans of the chest (upper and middle lung fields, in A and B, respectively) showing ground-glass opacities and patchy areas of consolidation in the lung periphery.

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Correlation vs. regression in association studies

Suzana Erico Tanni[1,2], Cecilia Maria Patino[1,3], Juliana Carvalho Ferreira[1,4]

When the goal of a researcher is to evaluate the relationship between variables, both correlation and regression analyses are commonly used in medical science. Although related, correlation and regression are not synonyms, and each statistical approach is used for a specific purpose and is based on a set of specific assumptions.

When testing the correlation between two variables, we use the correlation coefficient (r) to quantify both the strength and the direction of the relationship between two numeric variables, the results ranging from −1 to 1. When r = 0, this indicates that there is no linear relationship between the two variables; when r = 1, this indicates a perfect positive relationship between the two variables and implies that as the value of one variable increases, the value of the other one also increases (Figure 1). When r = −1, this indicates a perfect negative relationship and implies that as the value of one variable increases, the value of the other one decreases. In most cases, the strength of the relationship between the variables is not perfect; therefore, r is not exactly 1 or −1. The strength of a correlation is commonly interpreted as weak (r < ±0.4), moderate (r ranging from ±0.4 to ±0.7), and strong (r > ±0.7).[1] Lastly, we highlight that when correlation is used as a statistical approach, the data should be derived from a random sample; the variables should be continuous; the data should not include outliers; each pair of variables need to be independent[1]; and the correlation does not necessarily imply a cause-and-effect relationship.

Regression is indicated when one of the variables is an outcome and the other one is a potential predictor of that outcome, in a cause-and-effect relationship. If the outcome is a continuous variable, a linear regression model is indicated, and, if it is binary, a logistic regression is used. Regression also quantifies the direction and strength of the relationship between two numeric variables, X (the predictor) and Y (the outcome); however, in contrast with correlation, these two variables are not interchangeable, and correctly identifying the outcome and the predictor is key. Regression models additionally permit the evaluation of more than one predictor variable, another important difference from correlation analysis.[2]

Regression is a linear mathematical model represented by the equation $Y = \beta_0 + \beta_1 X$ (Figure 1). When the value of X (the predictor) is zero, the value of Y is β_0 (the line intercept), and β_1 is the slope, which gives us information of the magnitude and direction of the association between X and Y, similarly to the correlation coefficient. When $\beta_1 = 0$, there is no association between X and Y. When $\beta_1 > 0$ or $\beta_1 < 0$, the association between X and Y is positive or negative, respectively. Important assumptions of linear regression are normality and linearity of the outcome variable, independence between the two variables, and equal variance of the outcome variable across the regression line.[2]

In conclusion, when evaluating the relationship between two variables, we need to understand the differences between correlation and regression and choose which statistical test is better to answer the research question.

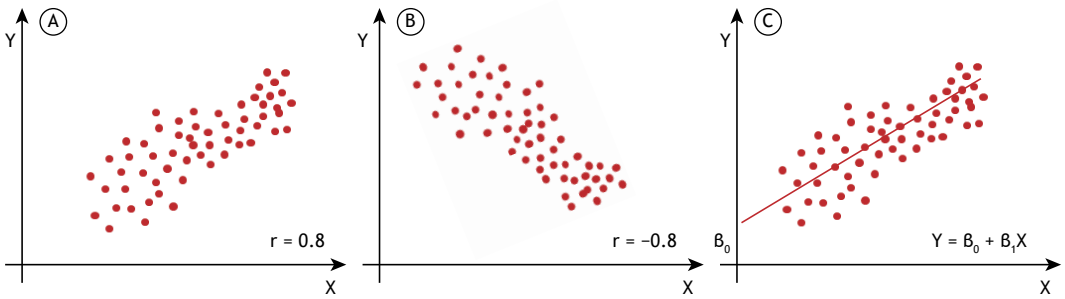

Figure 1. Scatter plots with simulated values of two variables, X and Y. In A, the circles represent pairs of simulated variables X and Y, showing that increases in X are associated with increases in Y: correlation coefficient (r) = 0.8. In B, the circles represent pairs of simulated variables X and Y, showing that increases in X are associated with decreases in Y: r = −0.8. In C, the circles represent the same pairs of simulated values of variables X and Y shown in A, fitted with a linear regression model, in which β_0 is the intercept and β_1 is the slope of the curve.

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Integrating measurements of pulmonary gas exchange to answer clinically relevant questions

José Alberto Neder[1], Danilo Cortozi Berton[2], Denis E O'Donnell[1]

BACKGROUND

The human body is primarily concerned with the stability of pH. The lungs are the organs responsible for maintaining an adequate $PaCO_2$ for the level of CO_2 production ($\dot{V}CO_2$) while avoiding critical decrements in PaO_2. Most of the pulmonary function tests, however, explore potential abnormalities in a step that precedes alveolar gas exchange, i.e., ventilation ($\dot{V}E$). Of note, arterial blood gases are influenced not only by the integrity of the alveolar-capillary membrane but also by hemodynamic factors (e.g., poor peripheral tissue perfusion leading to low mixed venous O_2 pressure) and changes in ventilatory drive (e.g., hypoventilation leading to hypercapnia and hypoxemia) among others.[1] Due to the ominous systemic consequences of impaired pulmonary gas exchange, tests addressing its multifaceted features are germane to the practice of Pulmonology.

OVERVIEW

A 71-year-old current smoker woman was referred to the pulmonology clinic due to progressing exertional dyspnea (modified Medical Research Council score = 3/4) despite normal spirometry, lung volumes, and contrast-enhanced chest CT results. Her dyspnea has been ascribed to sedentary lifestyle and severe anemia in the context of multiple myeloma. A six-minute walk test confirmed poor exercise tolerance with high dyspnea burden and exertional hypoxemia. Tests assessing gas exchange showed: a) low hemoglobin-corrected DL_{CO}

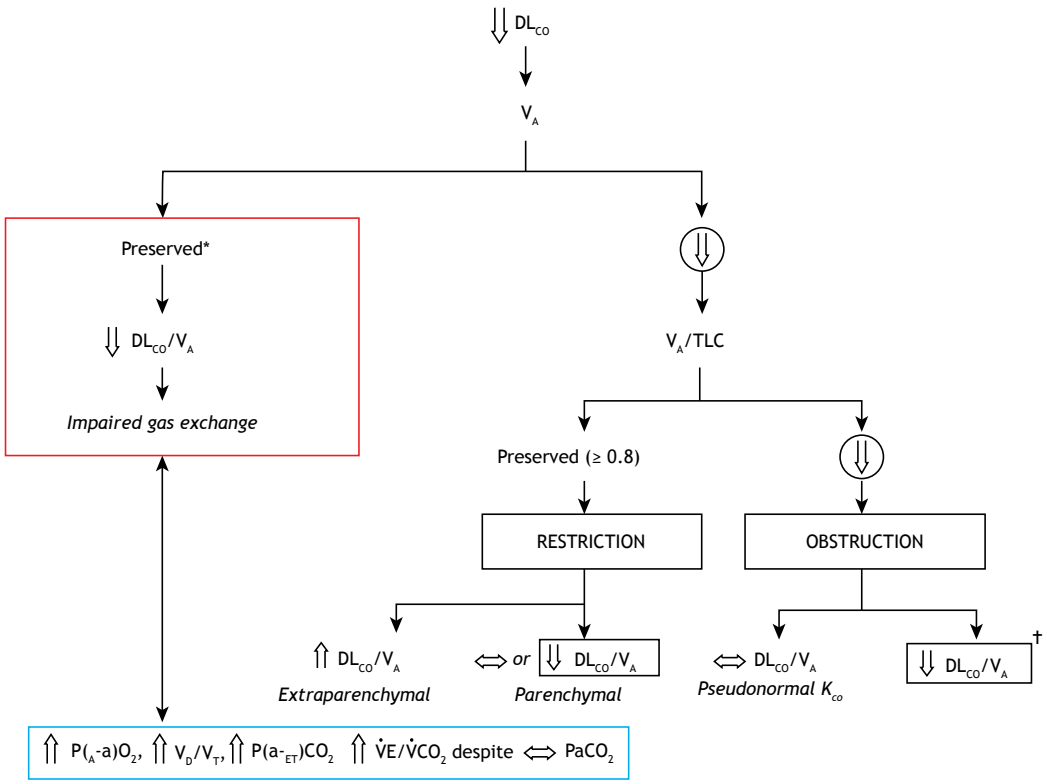

Figure 1. A simplified framework for an integrative analysis of pulmonary gas exchange based on routine pulmonary function tests. See text for further elaboration. Modified, with permission from the publisher.[3] V_A: alveolar ventilation; K_{CO}: carbon monoxide diffusion (transfer) coefficient; $P(A\text{-}a)O_2$: alveolar-arterial gradient pressure of O_2; V_D: dead space ventilation; V_T: tidal volume; $P(a\text{-}ET)CO_2$: arterial to end-tidal carbon dioxide gradient; $\dot{V}E$:ventilation; and $\dot{V}CO_2$: carbon dioxide production. *A normal V_A may coexist with airflow obstruction in a subject with mild airflow limitation in whom the distributive abnormalities are not severe enough to decrease V_A. †V_A may still lie in the normal range despite a low V_A/TLC in a severely hyperinflated patient (high TLC).

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and carbon monoxide transfer coefficient (K_{CO}) with normal alveolar ventilation (V_A) and V_A/TLC ratio; b) mildly reduced PaO_2 and eucapnia; and c) high alveolar-arterial gradient pressure of O_2 [$P(_A\text{-}a)O_2$], shunt fraction (on 100% O_2), physiological dead space, arterial to end-tidal carbon dioxide gradient [$P(a\text{-}_{ET})CO_2$], and resting o $\dot{V}E/\dot{V}CO_2$ratio. The pattern of impaired pulmonary gas exchange (Figure 1, in red), shunt and preserved $\dot{V}E$ distribution in the absence of emphysema or pulmonary arterial-venous fistulas raised concerns of poor pulmonary perfusion secondary to an extrapulmonary shunt. In fact, a transesophageal echocardiogram with microbubbles showed a small patent foramen ovale whose dimension markedly increased even with mild exertion. Absence of pulmonary hypertension at rest did not preclude right-to-left shunt (putative mechanisms in the study by Vitarelli).[2]

The rate of alveolar gas exchange can be substantially impaired despite preserved lung parenchyma. If hypoxemia cannot be explained by hypoventilation—high $PaCO_2$ and alveolar partial pressure of CO_2 (P_ACO_2), leading to low alveolar partial pressure of O_2 (P_AO_2)—or low inspired O_2 pressure (e.g., high altitude), impaired pulmonary perfusion should be considered as the most likely explanation. In the present case, right-to-left shunt diminished pulmonary perfusion thereby decreasing the functional surface for alveolar-capillary gas transfer ($\downarrow DL_{CO}$).[3] As VE was relatively well distributed (normal V_A/TLC ratio),[4] K_{CO} decreased. High $\dot{V}E$/perfusion ratio increased P_AO_2—and $P(_A\text{-}a)O_2$ as PaO_2 was low—and the fraction of tidal volume "wasted" in the dead space.[5] Thus, end-tidal CO_2 tension ($P_{ET}CO_2$) was substantially lower than P_ACO_2 (estimated by $PaCO_2$), because it was diluted by the PCO_2 from alveoli which were not properly exposed to CO_2-rich venous blood [$\uparrow P(a\text{-}_{ET})CO_2$].[6] Higher $\dot{V}E$ was then needed to keep alveolar ventilation ($\uparrow\dot{V}E/\dot{V}CO_2$ ratio; Figure 1, in blue).

CLINICAL MESSAGE

An integrated analysis of arterial blood gases (with indirect measurements of $\dot{V}E$ distribution and $\dot{V}E$-perfusion matching) and lung transfer capacity—in the light of clinical data—is invariably useful to untangle the mechanisms and consequences of impaired pulmonary gas exchange.

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Body mass index, asthma, and respiratory symptoms: a population-based study

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ABSTRACT

Objective: To estimate the prevalence of respiratory symptoms and asthma, according to body mass index (BMI), as well as to evaluate factors associated with physician-diagnosed asthma, in individuals ≥ 40 years of age. **Methods:** This was a population-based cross-sectional study conducted in Florianópolis, Brazil, with probability sampling. Data were collected during home visits. Demographic data were collected, as were reports of physician-diagnosed asthma, respiratory symptoms, medications in use, and comorbidities. Anthropometric measurements were taken. Individuals also underwent spirometry before and after bronchodilator administration. Individuals were categorized as being of normal weight (BMI < 25 kg/m^2), overweight (25 kg/m^2 ≥ BMI < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2). **Results:** A total of 1,026 individuals were evaluated, 274 (26.7%) were of normal weight, 436 (42.5%) were overweight, and 316 (30.8%) were obese. The prevalence of physician-diagnosed asthma was 11.0%. The prevalence of obesity was higher in women (p = 0.03), as it was in respondents with ≤ 4 years of schooling (p < 0.001) or a family income of 3-10 times the national minimum wage. Physician-diagnosed asthma was more common among obese individuals than among those who were overweight and those of normal weight (16.1%, 9.9%, and 8.0%, respectively; p = 0.04), as were dyspnea (35.5%, 22.5%, and 17.9%, respectively; p < 0.001) and wheezing in the last year (25.6%, 11.9%, and 14.6%, respectively; p < 0.001). These results were independent of patient smoking status. In addition, obese individuals were three times more likely to report physician-diagnosed asthma than were those of normal weight (p = 0.005). **Conclusions:** A report of physician-diagnosed asthma showed a significant association with being ≥ 40 years of age and with having a BMI ≥ 30 kg/m^2. Being obese tripled the chance of physician-diagnosed asthma.

Keywords: Obesity; Dyspnea; Cough; Asthma; Smoking.

INTRODUCTION

Asthma and obesity are common conditions that predominantly affect women and can coexist.[1] In recent years, a considerable number of studies have provided evidence that obesity and asthma are linked. Obesity has been reported as a risk factor for asthma in various demographic groups.[2,3] In addition, results from a meta-analysis involving more than 300,000 adults have shown that obesity nearly doubles the likelihood of incident asthma and that there is a dose-response effect of increasing body mass index (BMI) on asthma incidence.[4] Furthermore, obesity is associated with increased asthma severity, reduced disease control, and increased risk of exacerbations.[5,6] Factors contributing to the pathogenesis of asthma in obese individuals include changes in respiratory mechanics and altered inflammatory and immune responses because of obesity.[1,7]

Obesity has been associated with other chronic respiratory conditions.[8-11] Respiratory symptoms, such as dyspnea and exercise intolerance, are common in obese individuals[1,12] and are possibly due to body structure changes resulting from a sedentary lifestyle.[13] Studies have shown that the prevalence of obesity in Brazil has increased over the years. Malta et al.[14] used data from the Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases and examined trends in the prevalence of overweight and obesity in adults in 26 Brazilian state capitals and the Federal District of Brasília between 2006 and 2012. The authors reported that the prevalence of obesity increased from 11.6% in 2006 to 17.4% in 2012.

Few studies have examined trends in the prevalence of asthma in Brazil.[15-17] In a study conducted in Brazil and examining 2013 Brazilian National Health Survey data for 60,202 adults (in the 18- to 49-year age bracket), the prevalence of physician-diagnosed asthma was found to be 4.4%.[15] In addition, the study examined temporal trends in the prevalence of asthma, which was found

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to have remained stable in 1998, 2003, and 2008. Other studies, however, have shown that trends in the prevalence of asthma vary across Brazilian capitals, the prevalence of asthma increasing considerably each year in some cities, such as Florianópolis,[16] and remaining stable in others, such as Porto Alegre.[17]

Data on the prevalence of common chronic diseases such as asthma and obesity play an important role in guiding health policies and providing the basis for the development of educational interventions and preventive measures. Therefore, the objective of the present study was to estimate the prevalence of respiratory symptoms and asthma, according to BMI, as well as to evaluate factors associated with physician-diagnosed asthma, in individuals ≥ 40 years of age.

METHODS

This is a subanalysis of the *Respira Floripa* study, a population-based cross-sectional study conducted in the urban area of Florianópolis, with probability sampling of census tracts and households and data being collected during home visits, as described elsewhere.[18] The present study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina, in Florianópolis (Protocol 1136; FR: 385174; Certificate no. 766 Dec 31, 2010), and all participants gave written informed consent.

A detailed description of the methods used in the present study can be found elsewhere.[18,19] In brief, a representative sample of individuals ≥ 40 years of age residing in the greater metropolitan area of Florianópolis was randomly obtained.[18,19] The study consisted of one or more household visits. Eligible residents who agreed to participate in the study answered questions regarding demographic characteristics, respiratory symptoms, medication use and doses, and physician-diagnosed comorbidities. Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society standards,[20] with the use of an American Thoracic Society-certified, portable, ultrasound-based spirometer (EasyOne; ndd Medical Technologies, Inc., Andover, MA, USA). The reference values used were those of Hankinson et al.[21] Height was measured with a portable stadiometer (Seca®; Hamburg, Germany), and weight was measured with an electronic scale (Tanita Corporation of America, Inc., Arlington Heights, IL, USA). Height and weight were measured with participants barefoot and wearing light clothing.

On the basis of their BMI, participants were stratified into the following categories[22]: normal weight (20 kg/m^2 ≥ BMI < 25 kg/m^2), overweight (25 kg/m^2 ≥ BMI < 30 kg/m^2), and obesity (BMI ≥ 30 kg/m^2). Smoking status was determined in accordance with the criteria established by the Centers for Disease Control and Prevention.[23] Individuals who answered "yes" to the question "Has your doctor ever told you that you have asthma, wheezy bronchitis, or allergic bronchitis?" were considered to have physician-diagnosed asthma. Individuals with chronic airflow limitation (CAL), as determined by a post-bronchodilator FEV_1/FVC ratio of < 0.7, were considered to have COPD.[24] Individuals who answered "yes" to the question "Are there months in which you cough almost every day?" were considered to have chronic cough. Individuals who answered "yes" to the questions "Do you usually have phlegm in your chest that is difficult to expectorate, even when you do not have a cold?" and "Are there months in which you have this phlegm almost every day?" were considered to have chronic expectoration. Individuals who answered "yes" to the question "Do you have shortness of breath when hurrying on level ground or walking up a slight incline?" were considered to have dyspnea. Individuals who answered "yes" to the question "Have you had wheezing or whistling in the chest in the past 12 months?" were considered to have wheezing in the last year. Individuals who answered "yes" to at least one of the questions regarding respiratory symptoms were considered to have respiratory symptoms. The Brazilian Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used in order to determine the presence of symptoms of depression and anxiety,[25] which were considered to be present when the HADS score was ≥ 8.[26]

Statistical analysis

Continuous variables are summarized as means and standard deviations, and categorical variables are summarized as absolute and relative frequencies. Differences among groups regarding categorical variables were evaluated by the chi-square test. Comparison of means between two groups was performed with the Student's t-test. Comparison of means among three or more groups was performed with ANOVA, which was followed by post hoc analysis with the Bonferroni test (when necessary). Factors associated with self-reported physician-diagnosed asthma were analyzed with the use of generalized linear models (Poisson regressions with robust variance estimates). The risk factors examined were age, sex, self-reported race (White or Non-White), BMI (as above), level of education (≤ 4 years of schooling, 5-8 years of schooling, or ≥ 9 years of schooling, in accordance with the educational system in Brazil), smoking status (smokers/former smokers or nonsmokers), socioeconomic class (class A—a family income of > 20 times the Brazilian national minimum wage; class B—a family income of 11-20 times the Brazilian national minimum wage; class C—a family income of 4-10 times the Brazilian national minimum wage; class D—a family income of 2-3 times the Brazilian national minimum wage; and class E—a family income of ≤ 1 time the Brazilian national minimum wage), physician-diagnosed rhinitis, and physician-diagnosed gastritis, ulcer, or gastroesophageal reflux disease (GERD). Prevalence ratios and their 95% confidence intervals were used as a measure of effect size. Smoking, sex, age, level of education, and socioeconomic class were treated as covariates. All statistical tests were two-tailed, and the level of significance was set at $p < 0.05$. All statistical analyses were performed with the IBM

SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 1,059 adults participated in the study. Of those, 33 (3.1%) were excluded from the analysis because they had a BMI of < 20 kg/m^2. White individuals (85.4%), individuals ≥ 50 years of age (72.9%), females (59.6%), individuals with ≥ 9 years of schooling (57.3%), individuals belonging to socioeconomic class C (75.0%), and nonsmokers (82.7%) predominated. The prevalence of overweight was 42.5%, and the prevalence of obesity was 30.8%. The prevalence of self-reported asthma was 11.3%. Table 1 describes the characteristics of the study population, by BMI.

Prevalence of asthma, respiratory symptoms, and other respiratory diseases in normal-weight, overweight, or obese individuals

As can be seen in Figure 1, physician-diagnosed asthma was more common among obese individuals than among overweight individuals and those of normal weight (16.1%, 9.9%, and 8.0%, respectively; p = 0.004), as were dyspnea (35.5%, 22.5%, and 17.9%, respectively; p < 0.001) and wheezing in the last year (25.6%, 11.9%, and 14.6%, respectively; p < 0.001). In contrast, the prevalence of rhinitis was significantly higher in normal-weight individuals. There was a trend toward a higher prevalence of COPD among normal-weight individuals than among obese or overweight individuals (11.3%, 6.3%, and 8.3%, respectively; p = 0.09). The prevalence of chronic cough was similar among the groups, as was the prevalence of chronic expectoration. As can be seen in Table 2, the prevalence of dyspnea and that of wheezing increased significantly with increasing BMI, regardless of smoking status. In contrast, the prevalence of chronic expectoration was significantly higher in obese nonsmokers than in the remaining subgroups. The prevalence of physician-diagnosed asthma was highest in obese smokers, whereas the prevalence of rhinitis was highest in nonobese nonsmokers. Without considering smoking status, the prevalence of rhinitis

Table 1. Characteristics of the study population (N = 1,026), stratified into normal weight, overweight, and obesity categories on the basis of the body mass index.[a]

Characteristic	Normal weight (n = 274)	Overweight (n = 436)	Obesity (n = 316)	p
Age, years	57.0 ± 11.2	59.6 ± 12.2	57.3 ± 10.8	0.003
Sex				0.04
Female	162 (26.5)	244 (39.9)	206 (33.7)	
Male	112 (27.1)	192 (46.4)	110 (26.6)	
Self-reported race				0.9
White	234 (26.7)	374 (42.7)	268 (30.6)	
Non-White	40 (26.7)	62 (41.3)	48 (32.0)	
Level of education, no. of years of schooling				0.004
0-4	50 (19.5)	118 (45.9)	89 (34.6)	
5-8	41 (22.7)	77 (42.5)	63 (34.8)	
≥ 9	183 (31.1)	241 (41.0)	164 (27.9)	
Socioeconomic class				0.2
A or B	48 (32.4)	65 (43.9)	35 (23.6)	
C	198 (25.7)	326 (42.4)	245 (31.9)	
D or E	28 (36.7)	45 (41.3)	36 (33.0)	
Smoking status				0.04
Nonsmoker	128 (23.5)	239 (43.9)	178 (37.2)	
Smoker/Former smoker	146 (30.0)	197 (41.0)	138 (28.7)	
Anthropometric characteristics				
BMI, kg/m^2	23.1 ± 1.3	27.4 ± 1.4	34.1 ± 3.8	< 0.001*
Neck circumference, cm	35.0 ± 4.4	37.1 ± 3.6	39.8 ± 3.8	< 0.001*
Waist circumference, cm	82.8 ± 8.1	94.1 ± 8.6	107.2 ± 10.4	< 0.001*
Hip circumference, cm	92.2 ± 6.5	102.6 ± 7.5	113.6 ± 9.6	< 0.001*
Nonrespiratory comorbidities				
Systemic arterial hypertension[b]	53 (19.3)	168 (38.5)	179 (56.6)	< 0.001
Heart disease[b]	46 (15.7)	76 (17.4)	73 (23.1)	0.04
Diabetes[b]	24 (8.8)	47 (10.8)	59 (18.7)	< 0.001
Gastritis/ulcer/GERD[b]	90 (32.8)	130 (29.8)	113 (35.8)	0.2
Symptoms of depression[c]	43(15.7)	89 (20.4)	64 (20.3)	0.2

BMI: body mass index; and GERD: gastroesophageal reflux disease. [a]Values expressed as n (%) or mean ± SD. [b]Self-reported physician-diagnosed disease. [c]Hospital Anxiety and Depression Scale score ≥ 8. *p < 0.001 for all between-group comparisons.

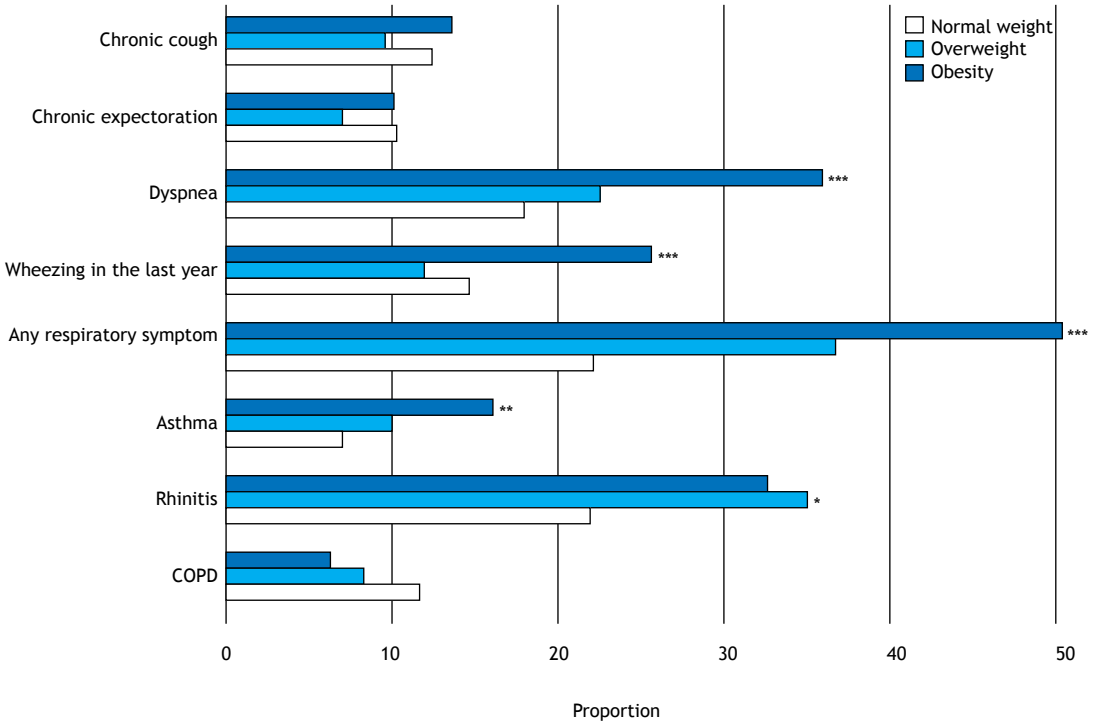

Figure 1. Prevalence of respiratory symptoms, asthma, rhinitis, and COPD in normal weight, overweight, and obesity groups. *p = 0.05; **p = 0.001; ***p < 0.001.

Table 2. Prevalence of respiratory symptoms, asthma, and respiratory disease in individuals of normal weight, overweight individuals, and obese individuals, by smoking status.

Prevalence	Normal weight (n = 274)	Overweight (n = 436)	Obesity (n = 316)	p*
Chronic cough, n (%)	34 (12.4)	42 (9.6)	43 (13.6)	0.2
Nonsmokers	6 (4.7)	16 (6.7)	18 (10.1)	0.1
Smokers/Former smokers	28 (19.2)	26 (13.2)	25 (18.1)	0.2
Chronic expectoration, n (%)	28 (10.2)	31 (7.1)	32 (10.1)	0.2
Nonsmokers	2 (1.6)	9 (3.8)	14 (7.9)	0.02
Smokers/Former smokers	26 (17.8)	22 (11.2)	18 (13.0)	0.2
Dyspnea, n (%)	48 (17.9)	98 (22.5)	113 (35.5)	< 0.001
Nonsmokers	13 (10.2)	44 (18.4)	56 (31.5)	< 0.001
Smokers/Former smokers	35 (24.0)	53 (26.9)	59 (42.8)	< 0.001
Wheezing in the last year, n (%)	40 (14.6)	52 (11.9)	81 (25.6)	< 0.001
Nonsmokers	10 (7.8)	15 (6.3)	38 (21.3)	< 0.001
Smokers/Former smokers	30 (20.5)	37 (18.8)	43 (31.2)	< 0.001
Any respiratory symptom, n (%)[a]	90 (22.0)	162 (37.2)	158 (50.0)	< 0.001
Nonsmokers	24 (18.8)	70 (29.3)	77 (43.3)	< 0.001
Smokers/Former smokers	66 (45.2)	92 (46.7)	81 (58.7)	0.04
Asthma, n (%)	22 (8.0)	43 (9.9)	51 (16.1)	0.004
Nonsmokers	9 (7.0)	20 (8.4)	25 (14.0)	0.07
Smokers/Former smokers	13 (8.9)	23 (11.7)	26 (18.8)	0.04
Rhinitis, n (%)	60 (21.9)	64 (34.8)	60 (32.6)	0.04
Nonsmokers	35 (27.3)	31 (13.0)	29 (16.3)	0.002
Smokers/Former smokers	25 (17.1)	33 (16.8)	31 (22.5)	0.4
COPD, n (%)	31 (11.3)	36 (8.3)	20 (6.3)	0.09
Nonsmokers	2 (1.6)	11 (4.6)	6 (3.4)	0.3
Smokers/Former smokers	29 (19.9)	25 (12.7)	14 (10.1)	0.04

[a]Any respiratory symptom: dyspnea, wheezing in the last year, chronic cough, or chronic expectoration.

was highest in overweight individuals. In contrast, the prevalence of COPD was significantly higher in smokers/former smokers of normal weight than in the remaining subgroups.

Reports of inhaled corticosteroid use or asthma medication use were more common among participants with physician-diagnosed asthma than among those without (18.8% vs. 0.6%, $p < 0.001$, and 34.2% vs. 1.3%, $p < 0.001$, respectively). In addition, post-bronchodilator percent predicted FEV_1, post-bronchodilator percent predicted FVC, and the FEV_1/FVC ratio were significantly lower in participants with physician-diagnosed asthma than in those without (79.9% ± 23.3% vs. 92.9% ± 18.0%, $p < 0.001$; 81.5% ± 15.2% vs. 89.2% ± 15.2%, $p < 0.001$; and 0.75 ± 0.10 vs. 0.80 ± 0.07, $p < 0.001$, respectively). However, 48 (41.4%) of all participants with physician-diagnosed asthma had normal spirometry results. Of those who had abnormal spirometry results (airflow limitation), 38.2% had a significant bronchodilator response (≥ 200 mL and ≥ 12%).

Relationship among physician-diagnosed asthma, smoking, and CAL

The relationship among physician-diagnosed asthma, smoking, and CAL is shown in Figure 2. Of the individuals with self-reported physician-diagnosed asthma, 24 (20.7%) had CAL, as determined by spirometry. Of the never smokers, 8 (14.8%) had CAL. Among smokers/former smokers with a smoking history of < 10 pack-years, the prevalence of CAL was 35.5%. Among those with a smoking history of 10-20 pack-years, the prevalence of CAL was 11.1%, whereas, among those with a smoking history ≥ 20 pack-years, the prevalence of CAL was 24.2%.

Prevalence of physician-diagnosed asthma and associated demographic and clinical variables

The prevalence of physician-diagnosed asthma was significantly higher in women, in individuals with 5-8 years of schooling, in individuals belonging to socioeconomic class C, and in obese individuals. Being obese tripled the chance of physician-diagnosed asthma (Table 3). In addition, the prevalence of physician-diagnosed asthma was significantly higher in individuals with COPD and in those with physician-diagnosed gastritis, ulcer, or GERD (Table 3). Multivariate analysis adjusted for age, sex, level of education, socioeconomic class, smoking, and the remaining variables showed that self-reported physician-diagnosed rhinitis, overweight, and obesity (BMI ≥ 30 kg/m^2) were independently associated with self-reported physician-diagnosed asthma (Table 4).

DISCUSSION

The results of the present study show that the prevalence of asthma and that of obesity are high in individuals ≥ 40 years of age, and that respiratory symptoms and asthma are significantly more common in obese individuals. The results also show that being obese tripled the chance of physician-diagnosed asthma.

The association between asthma and BMI is complex and has been widely studied. The findings of the present study are consistent with those of epidemiological studies showing that being obese doubles the risk of incident asthma.[4] Population-based studies evaluating the association between asthma and obesity are scarce, particularly in Brazil. To our knowledge, this is the first population-based study in Brazil involving adults ≥ 40 years of age and investigating the association among obesity, asthma, and respiratory symptoms. In the present study, the prevalence of respiratory symptoms such as dyspnea and wheezing in the last year was significantly more common in obese individuals than in nonobese individuals regardless of smoking status, constituting further evidence for the association between obesity and physician-diagnosed asthma. This association is further supported by the fact that the probability of physician-diagnosed asthma was 2.5 times higher in individuals with physician-diagnosed

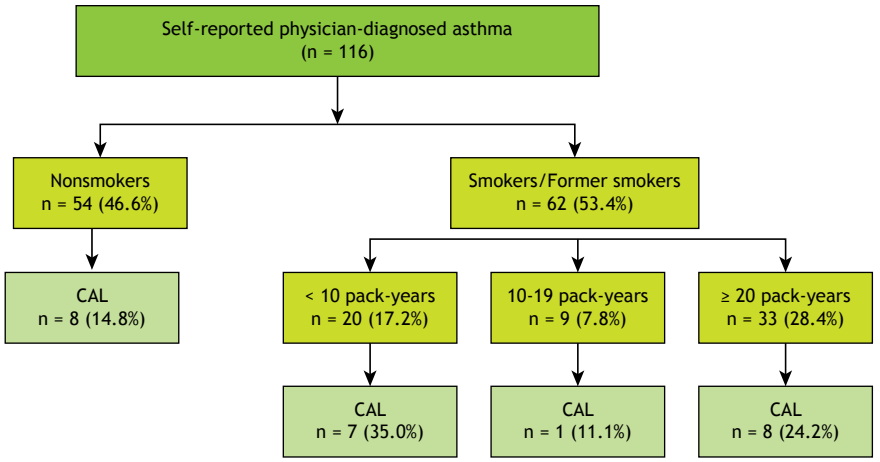

Figure 2. Prevalence of chronic airflow limitation (CAL) in nonsmokers and smokers/former smokers with physician-diagnosed asthma.

Table 3. Self-reported physician-diagnosed asthma, by demographic and clinical variables (and their respective prevalence ratios).

Variable	n/N	%	Crude analysis		Adjusted analysis	
			PR (95% CI)	p	PR (95% CI)	p
Sex						
Female	83/612	13.6	1	0.007	1	< 0.001*
Male	33/414	8.0	1.7 (1.1-2.5)		1.6 (1.3-2.2)	
Age bracket, years						
40-49	39/278	14.0	1		1	
50-59	29/313	9.3	1.2 (0.8-1.8)	0.2	1.3 (0.9-2.1)	0.1**
≥ 60	48/435	11.0	0.8 (0.5-1.3)		0.8 (0.5-1.4)	
Self-reported race						
White	94/976	10.7	1	0.1	1	0.1**
Non-White	22/150	14.7	1.4 (0.9-2.1)		1.4 (0.9-2.2)	
Level of education, no. of years of schooling						
0-4	26/257	10.1	0.8 (0.7-1.6)		1.1 (0.7-1.8)	
5-8	28/181	15.5	1.5 (0.9-2.5)	0.8	1.4 (0.8-2.4)	0.8**
≥ 9	62/588	10.5	1		1	
Socioeconomic class						
A or B	8/148	5.4	1		1	
C	100/769	13.0	2.4 (1.2-4.8)	0.01	2.4 (1.2-4.9)	0.01**
D or E	8/109	7.3	1.3 (0.5-3.5)		1.3 (0.5-3.5)	
BMI, kg/m^2						
< 25	22/274	8.0	1		1	
25-29	43/436	9.9	1.2 (0.7-2.0)	0.004	1.1 (0.7-1.9)	0.002**
≥ 30	51/316	16.1	2.0 (1.2-3.2)		2.1 (1.3-3.4)	
Smoking status						
Nonsmokers	54/545	9.9	1	0.1	1	0.5**
Smokers/former smokers	62/481	12.9	1.3 (0.9-1.9)		1.3 (0.8-2.2)	
Rhinitis[a]						
No	70/842	8.3	1	< 0.001		< 0.001**
Yes	46/184	25.0	3.0 (2.1-4.2)		2.1 (1.4-3.1)	
Gastritis/ulcer/GERD[a]						
No	59/693	8.5	1	< 0.001	1	0.001**
Yes	57/333	17.1	2.0 (1.4-2.8)		1.9 (1.3-2.7)	

PR: prevalence ratio; BMI: body mass index; and GERD: gastroesophageal reflux disease. [a]Self-reported physician-diagnosed disease. *Adjusted for BMI, smoking, and age. **Adjusted for sex, BMI, smoking, and age.

rhinitis and 1.5 times higher in individuals with physician-diagnosed gastritis, ulcer, or GERD. This is not unexpected, given that these comorbidities are commonly associated with asthma.[27]

In the present study, asthma treatment was more common in individuals with physician-diagnosed asthma than in those without, the former showing functional changes consistent with asthma. Taken together, these findings add robustness to the results of the present study. However, our results should be interpreted with caution because the presence of asthma in our cohort was determined by self-reports of physician-diagnosed asthma rather than by objective measures, meaning that there is a risk of overdiagnosis or underdiagnosis.[28]

Physician-diagnosed asthma is commonly used in order to define the presence of asthma in epidemiological studies.[14,15,29,30] In the present study, all participants underwent spirometry. Of those who reported having physician-diagnosed asthma, 58.6% had airflow limitation. Of those, 39.2% had a significant bronchodilator response. However, a significant proportion (41.4%) had normal spirometry. The presence of normal spirometry and absence of significant bronchodilator response do not rule out asthma.[31] Because this was a population-based study, it would have been impracticable to use additional methods to confirm the presence of asthma. In addition, there is sufficient evidence that a negative challenge test result rules out asthma as a cause of current respiratory symptoms but does not rule out a previous diagnosis of asthma. Because airway hyperresponsiveness varies as does asthma, prevalence estimates based on challenge test results are not adequate to rule out a previous diagnosis of asthma.[31] In summary, the definition of asthma in the present study is perfectly adequate for the objectives and design of the study.

Asthma and smoking are common conditions that can coexist in patients, and the prevalence of smoking

Table 4. Multivariate analysis of factors associated with self-reported physician-diagnosed asthma in individuals ≥ 40 years of age.

Factor	PR	95% CI	p*
Overweight	2.3	1.2-4.5	0.01
Obesity	3.1	1.6-6.0	0.001
Self-reported physician-diagnosed rhinitis	2.6	1.7-3.7	< 0.001

PR: prevalence ratio. *Adjusted for age, sex, level of education, socioeconomic class, and smoking.

in asthma patients has been reported to be similar to the prevalence of smoking in the general population.[32] Smoking has a negative impact on asthma, interfering with the response to corticosteroids and being associated with accelerated decline in lung function and increased exacerbations.[32-34] Although only a minority of the participants with physician-diagnosed asthma were current smokers, more than half had experimented with smoking. Because asthma is associated with accelerated decline in lung function regardless of smoking status, asthma patients with CAL were evaluated in the present study. Of those, one third had never smoked, and one third had a smoking history of < 20 pack-years. However, the presence of CAL in smokers/former smokers (13.3%) is suggestive of asthma-COPD overlap syndrome. This prevalence is higher than that reported in a recent study conducted in low-income countries.[29] However, differences between studies in populations and definitions of CAL might explain these discrepancies.

The prevalence of obesity in the present study was higher than the national prevalence reported in 2017.[14] Our results are similar to those reported in a study conducted in the city of São Paulo, Brazil,[35] where the prevalence of overweight and obesity was higher than the national prevalence. Methodological differences can explain the discrepancy. Malta et al.[14] assessed the prevalence of obesity in 26 Brazilian state capitals and in the Federal District of Brasília on the basis of data on height and weight collected via telephone interviews, whereas, in the present study and in the study conducted in São Paulo,[35] height and weight were objectively measured.

Our study has limitations, some of which are due to its design. As is the case with all studies in which a cross-sectional design is used, it is impossible to infer causality. Another limitation is the use of self-reports of physician-diagnosed asthma to define the presence of asthma in the present study. However, as discussed earlier, self-reported physician-diagnosed asthma is commonly used in order to define asthma in epidemiological studies. In addition, our definition of asthma was validated, at least in part, by our findings of differences in lung function between individuals with asthma and those without. Despite these limitations, the study methods and random selection of a representative sample add robustness to the results.

Respiratory symptoms in obese individuals should be objectively investigated in order to confirm or rule out asthma as a cause. If the presence of asthma is confirmed, personalized asthma treatment can provide better symptom control. Despite the role of genetic factors in these diseases, obesity prevention and treatment can minimize complications. Government policies and public health policies should work in concert to encourage lifestyle changes and healthy behaviors.

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Robotic thoracic surgery for resection of thymoma and tumors of the thymus: technical development and initial experience

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ABSTRACT

Objective: To evaluate the results of resection of tumors of the thymus by robotic thoracic surgery, analyzing the extent of resection, postoperative complications, time of surgery, and length of stay. **Methods:** Retrospective study from a database involving patients diagnosed with a tumor of the thymus and undergoing robotic thoracic surgery at one of seven hospitals in Brazil between October of 2015 and June of 2018. **Results:** During the study period, there were 18 cases of resection of tumors of the thymus: thymoma, in 12; carcinoma, in 2; and carcinoid tumor, in 1; high-grade sarcoma, in 1; teratoma, in 1; and thymolipoma, in 1. The mean lesion size was 60.1 ± 32.0 mm. Tumors of the thymus were resected with tumor-free margins in 17 cases. The median (interquartile range) for pleural drain time and hospital stay, in days, was 1 (1-3) and 2 (2-4), respectively. There was no need for surgical conversion, and there were no major complications. **Conclusions:** Robotic thoracic surgery for resection of tumors of the thymus has been shown to be feasible and safe, with a low risk of complications and with postoperative outcomes comparable to those of other techniques.

Keywords: Thymoma; Thymus neoplasms; Thymectomy; Thoracic surgery; Robotic surgical procedures.

INTRODUCTION

Thymomas and other tumors of the thymus are relatively rare neoplasms. Their treatment usually involves resection of the thymus and adjacent mediastinal fat. They are associated with paraneoplastic syndromes, the most common being myasthenia gravis, which is present in approximately one third of patients with thymoma.[1] Surgical treatment is indicated for the treatment of stage I and II thymomas, with a 10-year survival rate of 70-90%.[2] In more advanced stages and in cases of tumor recurrence, surgical resection, in combination with chemoradiotherapy, is indicated for local control of the disease.[3,4]

In the 1990s, the concept of minimally invasive surgery was introduced into the field of thoracic surgery and began to be applied in mediastinal surgical resections. The use of minimally invasive thymectomy was motivated by the possibility of minimizing the deleterious effects of prolonged general anesthesia and the postoperative pain caused by thoracotomy in patients with myasthenia gravis. In this context, studies have proven total thymectomy by video-assisted thoracoscopic surgery to be feasible in patients with myasthenia gravis[5] and also for those with stage I and II thymomas.[6] Since the beginning of the 21st century, robotic surgery has emerged as an interesting alternative because it not only offers the advantages of being minimally invasive but also provides a wider range of motion to the surgical performance, reduces the impact of surgeon hand tremors, enables greater precision in the movement of the forceps, and provides better three-dimensional visualization of the surgical field.[7,8]

In Latin America, especially in Brazil, minimally invasive thoracic surgery has recently come to be more widely used.[9] However, in contrast to the literature on pulmonary resections,[10] there is a lack of studies describing the results of resection of thymic tumors by robotic surgery. The primary objective of the present study was to evaluate the results of the resection of thymic tumors with the aid of robotics by determining the extent of resection, postoperative complications, operative time, and length of hospital stay.

METHODS

This was a retrospective study of patients diagnosed with a thymic tumor who underwent resection by robotic

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thoracic surgery. Every procedure was performed by the same group of surgeons, at one of seven hospitals in Brazil, and the lead author participated in all of them, either as the surgeon operating the console or as the proctor. The robotic platform used was the da Vinci Intuitive Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA). The hospitals involved were the São Paulo State Cancer Institute, *Hospital Sírio-Libanês*, *Hospital Albert Einstein*, *Hospital Nove de Julho*, and *Hospital São Luiz*, all located in the city of São Paulo, as well as the *Hospital Copa Star* and *Hospital Quinta D'Or*, both located in the city of Rio de Janeiro. All of the surgical procedures were performed between October of 2015 and June of 2018.

Data were collected from a database dedicated to robotic surgery and maintained by our team of thoracic surgeons. We included all cases of thymic tumors treated surgically during the period and excluded only patients whose medical records did not present information regarding sociodemographic data and histological type. Our eligibility criteria for robotic resection of mediastinal tumors were as follows: the patient being considered a candidate for the proposed procedure, on the basis of the clinical and anesthetic evaluation; the tumor being in the thymus; and there being no signs of invasion of adjacent structures such as the heart and great vessels. Tumor invasion of the pericardium or lung was not considered a contraindication to the robotic procedure. Figure 1 shows HRCT images of 2 patients with thymic tumors.

The surgical technique used was based on the description provided in a study conducted by Rueckert et al.[10] When that technique is employed, access to the mediastinum is preferentially through the left side of the chest (Figures 2 and 3). However, in some cases, the position of the tumor may necessitate right-sided access. The patient is placed in the supine position with the head rotated 30° to the contralateral side. Three surgical incisions are made for the ports, which are used for the robotic arms (one for the three-dimensional vision and two for the robotic forceps) positioned in the 3rd, 4th and 5th intercostal spaces (Figure 2). We also use an additional port for the assistant surgeon, who remains with the patient during surgery.

The surgery begins with the identification of the left phrenic nerve (Figure 3A) and subsequent opening of the mediastinal pleura anterior to it. Subsequently, loose connective tissue adjacent to the lesion is dissected until the mediastinal structures such as the pericardium, aorta, and innominate vein are completely exposed (Figure 3B). Complete resection of the thymus or resection of only the thymic tumor may then be performed.[11]

The variables evaluated in the present study were related to the surgical technique (operative time and partial or complete thymic tissue resection), perioperative outcomes (length of ICU stay, length of hospital stay, duration of pleural drainage, and postoperative complications), and the extent of the resection.

Total operative time was defined as the time from the initial incision to the final closure, including the creation of the ports, robot docking, console operation, and chest wall closure. The drainage time, length of ICU stay, and length of hospital stay were measured in days from the day of surgery, which was designated (D0), the subsequent days being designated D1, D2, etc. The discharge date was defined as the day on which the patient left the hospital, regardless of the time of discharge.

The extent of surgical resection was assessed by review of the pathology report. If the surgical specimens showed tumor-free margins or margins coincident with structures that precluded further resection, such as the sternum, pleural surface, or pericardium, the resection was categorized as curative (R0).[12] The thymomas were staged according to the Masaoka-Koga classification.[13]

Statistical analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). Categorical variables are expressed as absolute and relative frequencies. Type I error was set at 5%.

RESULTS

During the study period (from October of 2015 to June of 2018), 243 robotic procedures were performed by our group. Of those, 52 were resections of mediastinal lesions, including 33 of the anterior mediastinum, of which 18 were primary tumors of the thymus.

Of the patients with thymic tumors, half were male, and the mean age of the patients was 47.0 ± 12.1 years. The histological types found are described in Table 1. The mean size of the lesions, according to the pathology reports, was 60.1 ± 32.0 mm.

The surgical technique employed was that described by Rueckert et al.,[10] which utilizes three robotic arms and a secondary access for the auxiliary port. In the original technique, the preferential approach to the mediastinum is from the left side. However, in 6 of our cases, the location of the tumor dictated that the access be from the right side, and the robot was therefore positioned on that side. Total thymectomy associated with tumor resection was performed in 9 patients. The median total operative time and console time were 130 min (IQR: 90-156 min) and 72 min (IQR: 52.5-102.5 min), respectively. No significant intraoperative accidents were observed, nor was it necessary to convert to video-assisted surgery or open surgery in any of the cases.

Postoperatively, patients were hospitalized for 2-4 days (median = 2 days). Surgical recovery was in the ICU in 6 cases, the mean length of ICU stay being 1.1 days. Drainage time ranged from 1-3 days (median = 1 day).

The only early complication observed in our study was elevation of the hemidiaphragm, in 2 cases

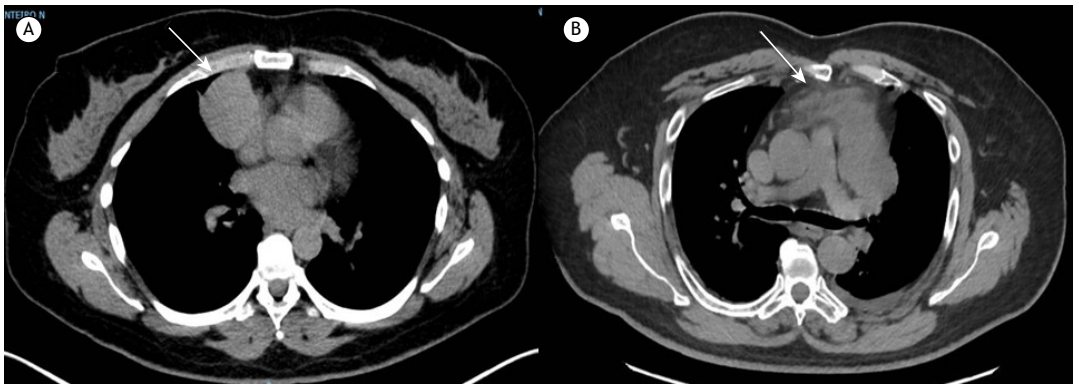

Figure 1. Chest HRCT. In A, a 47-year-old female patient with a history of papillary thyroid carcinoma (18 years earlier) and a right paracardiac mediastinal mass of 54 mm. Histological diagnosis of B1/B2 thymoma, Masaoka-Koga stage I classification. In B, a 59-year-old male patient with a left anterior mediastinal mass of 82 mm. Histological diagnosis of high-grade thymic sarcoma.

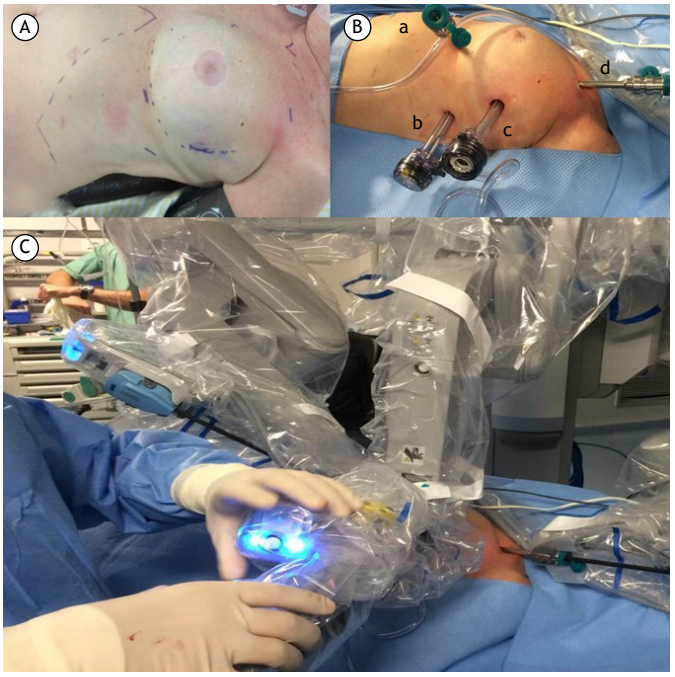

Figure 2. Positions of the robotic ports. In A, preoperative demarcation of the costal spaces and incision sites. In B, surgical ports before robot docking (a, arm 1; b, auxiliary port; c, camera; and d, arm 2). In C, robotic arms coupled to ports after docking.

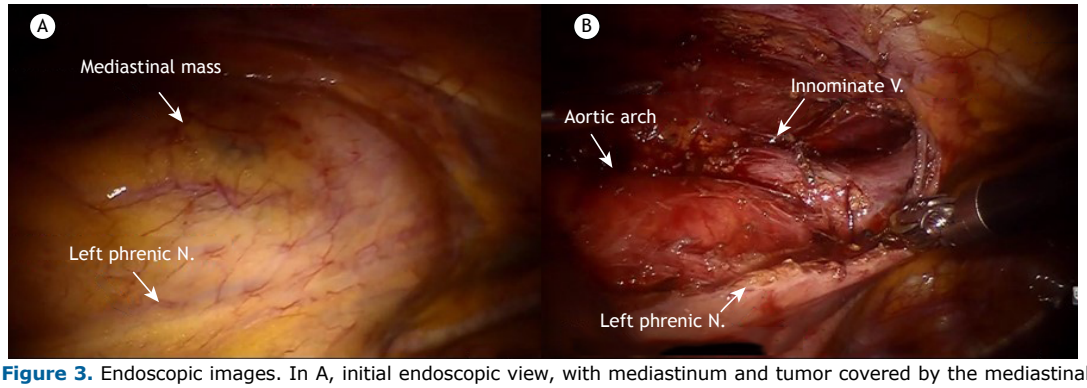

Figure 3. Endoscopic images. In A, initial endoscopic view, with mediastinum and tumor covered by the mediastinal pleura, identifying the left phrenic nerve in advance of the opening of the pleura and beginning of the dissection. In B, the surgical site after thymectomy and thymoma resection, with the mediastinal structures being visualized. N.: nerve; and V.: vein.

Table 1. Histological types of thymic tumors, operative times and postoperative data.

Thymic tumors resected by robotic thoracic surgery									
Histological type	Cases	Case No.	Histology	Masaoka-Koga Classification	Size, mm	Total operative time, min	Console time, min	Drainage time, days	Length of hospital stay, days
Thymoma	12	17	AB	IIa	76	80		1	2
		20	B1	I	30			1	2
		82	B1 (70%) B2 (30%)	I	54	140	90	1	2
		83			8,5	235	200	2	4
		138	B2	I	50	110	85	1	3
		159	AB	IIa	40	100	59	1	2
		180	B2	IVa	84			3	4
		185	AB	I	61	79	47	1	3
		187	B2	I	53			2	4
		190	B2	IIa	90	135	100	1	2
		221	AB	IIa	100	140	100	1	2
		237	AB	I	17	75	30	1	2
Thymic carcinoma	2	116			17	100	60	1	2
		153			90	85	55	1	2
Thymic carcinoid tumor	1	160			20	94	77	1	2
High-grade thymic sarcoma	1	172			82	260	210	2	3
Mature thymic teratoma	1	228			85	90	50	1	2
Thymolipoma	1	240			125	130	70	1	2

(11%). However, it had no clinical repercussions for the affected patients. One patient required readmission due to chylothorax diagnosed one month after surgery and was treated by thoracic duct embolization. There were no deaths in the present study.

Among all the resected tumors, compromised margins were described in the pathology report in only 1 case (5%), which was in a patient with thymoma. In that case, the margin was focally coincident with the area of the encapsulated neoplasm. Therefore, after a multidisciplinary discussion, the decision was made to administer adjuvant radiotherapy. The patient with a thymic carcinoid tumor presented signs of locoregional recurrence three months after surgery and underwent systemic treatment. At this writing, the patient was awaiting additional local treatment with surgery or radiotherapy. Lymph nodes were resected from at least one lymph node chain in 7 patients (mean, 3.4 lymph nodes/patient).

Of the 12 thymomas evaluated, 11 were categorized in the pathology examinations according to the Masaoka-Koga classification[13], as follows: stage I, in 6; stage IIa, in 4; and stage IVa, in 1. The patient with stage IVa thymoma was diagnosed intraoperatively with an anterior mediastinal tumor (Figure 4) and therefore underwent two surgical procedures. The first procedure was aborted after the identification of pleural implants and positive frozen section analysis results for neoplasia, after which the patient was submitted to neoadjuvant chemotherapy, resulting in a partial tumor response. The second procedure was performed four months later for complete resection of the thymoma, which presented local invasion of the lung and pleura.

In our sample, 4 patients received multimodal treatment and neoadjuvant chemotherapy. Of those 4 patients, 3 were diagnosed with thymoma and 1 was diagnosed with thymic carcinoma. Another patient received adjuvant radiotherapy after thymoma resection.

DISCUSSION

We have shown that the resection of thymic tumors by robotic surgery is feasible and safe. The implementation of a surgical technique in daily practice is a challenge, because the expectation is to achieve results comparable to those of medical centers where the technique is already well-established, although the experience of a team is based on its learning curve. Like our group, others have published their experiences with robotic surgery, reporting similar results.[14,15]

At the beginning of their robotic surgery program, Brown et al.[16] considered thymectomy to be the surgery of choice, because of the location of the thymus in the anterior mediastinum. Nevertheless, only 5 (10%)

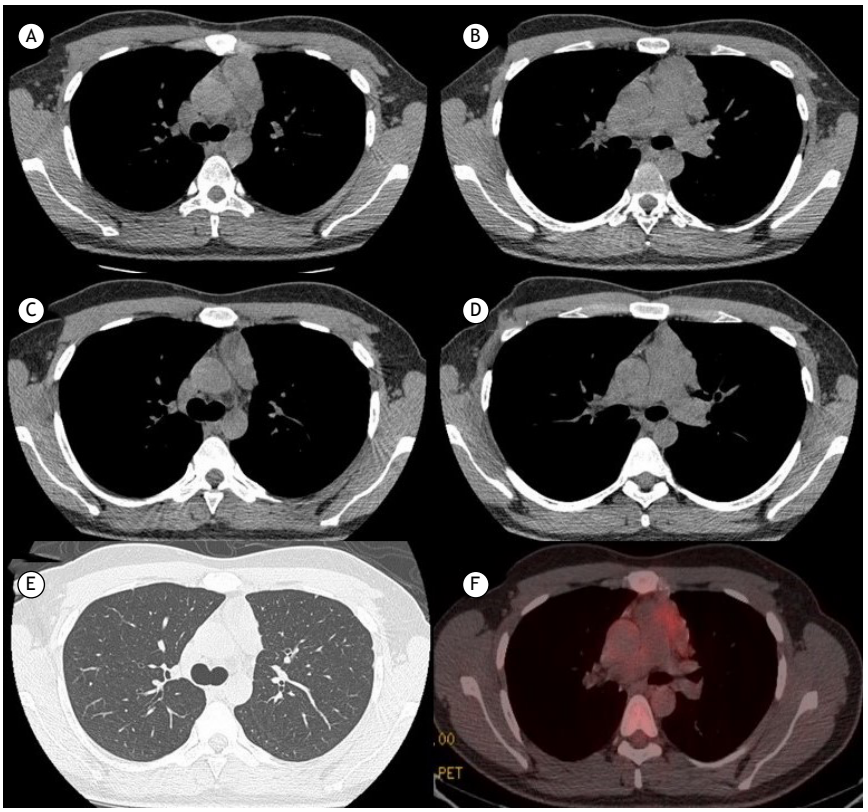

Figure 4. HRCT (A-E) and proton emission CT images (F) of the chest. In A and B, images of the thymoma in the initial preoperative evaluation. In C, D and E, images after neoadjuvant chemotherapy. In F, image of the thymoma after neoadjuvant treatment.

of our first 50 procedures were performed for the resection of mediastinal lesions. That is explained by the fact that our robotic thoracic surgery program was initially implemented at the São Paulo State Cancer Institute, where a prospective study was conducted to draw comparisons between pulmonary lobectomy performed by video-assisted thoracic surgery and pulmonary lobectomy performed by robotic thoracic surgery,[17] during which the surgeons in our group obtained their initial training and experience. That may have contributed to the fact that our operative time and perioperative outcomes were consistent with those reported by other groups with more experience in robotic surgery of the mediastinum.[18,19]

Following current trends, a systematic review published in 2018[20] proposed that minimally invasive surgery, including video-assisted thoracic surgery and robotic thoracic surgery, should be considered the surgical technique of choice in the treatment of early-stage thymic tumors. Minimally invasive treatment is associated with shorter hospital stays, less intraoperative bleeding, and better aesthetic results. In the present study, we showed that robotic surgery is associated with a shorter duration of pleural drainage and a shorter hospital stay, with medians of 1 and 2 days, respectively. In addition, minimally invasive surgery has been shown to be as effective as open surgery in terms of the rates of complications, local recurrence, and survival.[20] In the present study, the follow-up period was too short to allow us to estimate cancer outcomes. However, the low risk of complications was confirmed, given that only one complication (late chylothorax) was observed and none of the patients required reoperation.

As evidenced in studies on complications after mediastinal lymphadenectomy, chylothorax after thoracic surgery presents a good response to conservative treatment or embolization because it is a chylous fistula resulting from thoracic duct collaterals,[21] that is, of low output.

Regardless of the access route, the importance of complete tumor resection in terms of prognosis is known[22]; as such, all efforts should be directed to the total resection of the tumor and surrounding thymic tissue by avoiding direct manipulation to prevent capsule rupture and the spread of the tumor in the location. In our study, only 1 case did not present tumor-free margins after histopathological analysis, which was focally coincident with the encapsulated area of the tumor. The patient received adjuvant radiotherapy and, at the time of writing, had no evidence of disease recurrence 3 years after surgery. The technical advantages of robotic surgery were remarkable for the safe dissection of the mediastinal structures, notably the superior poles of the thymus.

Three-dimensional vision and traction through the use of grasping forceps on the robot's left arm, combined with the ability to perform precise movements within delicate cervical structures, contributed to the absence of vascular accidents or the need for surgical conversion in our study.

As shown in previous publications, resection of large thymic tumors by robotic surgery is safe and effective.[12,23] In our study, large tumors (largest diameter: 12.5 cm) were resected, which corroborates the hypothesis that size should not be considered an absolute contraindication to the method. Currently, the major limitation in cases of mediastinal lesions is the invasion of vascular structures, because the use of robots has not been proven safe in those cases.

Although robotic thoracic surgery has attracted great interest from many surgeons, its cost is still a limiting factor for the rapid spread of the technique. There are costs in several spheres, including the purchase of the robot, the maintenance and purchase of resources such as tweezers and disposable materials, and surgeon-specific training and certification to operate the robot. Although some studies show evidence of the economic advantage of robotic surgery, it is necessary for good perioperative outcomes, such as reduced complications and length of hospital stay, to contribute to the reduction of the total cost.[24] This is directly related to the experience of the surgeon, who must overcome the learning curve and obtain better results. Future perspectives show the tendency for more institutions to believe in the evolution of technology and, thus, invest in minimally invasive robotic surgery, which contributes to the improvement of patient care. At the same time, thoracic surgeons are motivated to become specialized in reproducing results achieved in established medical centers.

We can conclude that robotic thoracic surgery is safe and feasible in the treatment of thymic tumors by presenting a low risk of complications and a short length of hospital stay. The learning curve and cost are still limiting factors for the spread of the technique, which has a promising future.

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ORIGINAL ARTICLE

Robotic thoracic surgery for non-small cell lung cancer: initial experience in Brazil

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ABSTRACT

Objective: To describe the morbidity, mortality, and rate of complete resection associated with robotic surgery for the treatment of non-small cell lung cancer in Brazil, as well as to report the rates of overall survival and disease-free survival in patients so treated. **Methods:** This was a retrospective study of patients diagnosed with non-small cell lung carcinoma and undergoing resection by robotic surgery at one of six hospitals in Brazil between February of 2015 and July of 2018. Data were collected retrospectively from the electronic medical records. **Results:** A total of 154 patients were included. The mean age was 65 ± 9.5 years (range, 30-85 years). The main histological diagnosis was adenocarcinoma, which was identified in 128 patients (81.5%), followed by epidermoid carcinoma, identified in 14 (9.0%). Lobectomy was performed in 133 patients (86.3%), and segmentectomy was performed in 21 (13.7%). The mean operative time was 209 ± 80 min. Postoperative complications occurred in 32 patients (20.4%). The main complication was air leak, which occurred in 15 patients (9.5%). The median (interquartile range) values for hospital stay and drainage time were 4 days (3-6 days) and 2 days (2-4 days), respectively. There was one death in the immediate postoperative period (30-day mortality rate, 0.5%). The mean follow-up period was 326 ± 274 days (range, 3–1,110 days). Complete resection was achieved in 97.4% of the cases. Overall mortality was 1.5% (3 deaths), and overall survival was 97.5%. **Conclusions:** Robotic pulmonary resection proved to be a safe treatment for lung cancer. Longer follow-up periods are required in order to assess long-term survival.

Keywords: Lung neoplasms/surgery; Lung neoplasms/mortality; Robotic surgical procedures.

INTRODUCTION

In the last two decades, minimally invasive surgery has been established as the gold standard for the treatment of lung cancer.[1,2] Several studies have been published and confirmed the role of video-assisted thoracoscopic surgery in complex resections such as lobectomies and pneumonectomies.[3,4] Recently, robotic surgery has emerged as an alternative to conventional video-assisted thoracoscopic surgery, because it has the advantage of increasing the amplitude and precision of intracavitary maneuvers and movements, as well as improving visualization through three-dimensional imaging.[1] The use of robotics in thoracic surgery has been established in studies that demonstrated its feasibility, especially for mediastinal tumors and pulmonary resections, such as pulmonary lobectomy and segmentectomies.[5-7]

Although the use of robotics in thoracic surgery is still in its early stages, it is promising. Large case series have shown good results regarding postoperative morbidity and mortality, as well as length of hospital stay and the need for readmission.[5-7] Studies have shown the superiority of robotic surgery over traditional thoracotomy.[5] However, the concrete benefits of robotic surgery over conventional video-assisted thoracoscopic surgery are still the subject of study.[6,7] In addition, the costs related to robotic surgery are still one of the determining factors in choosing the method.[8]

The financial issue related to robotic surgery is particularly relevant in low- and middle-income countries, where resources are limited. Therefore, an analysis of the cost-effectiveness of the use of new techniques is essential. In Brazil, the first robotic thoracic surgical procedures were performed in 2010. However, the first case series describing pulmonary resections was published in 2016 and essentially demonstrated the feasibility of the method.[1] Nevertheless, data on the

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short- and medium-term results of this technique in our country are lacking. Therefore, the main objective of the present study was to describe the morbidity, mortality, and complete resection associated with robotic surgery for the treatment of non-small cell lung cancer in Brazil. The secondary objective was to report the rates of overall survival and disease-free survival in patients so treated.

METHODS

This was a retrospective study of patients diagnosed with non-small cell lung carcinoma and undergoing resection by robotic surgery between February of 2015 and July of 2018 by a group of thoracic surgeons at the São Paulo State Cancer Institute, Hospital Sírio-Libanês, Hospital Albert Einstein, Hospital Nove de Julho, and Hospital São Luiz, all located in the city of São Paulo, as well as the Hospital Copa Star/Rede D'Or, located in the city of Rio de Janeiro.

Selection of patients and data collection

We included all patients who underwent surgical resection of lung cancer by robotic surgery (segmentectomy, lobectomy, or bilobectomy) during the study period. Patients who underwent wedge surgical resection were excluded, as were those for whom the medical records were incomplete. Data were collected retrospectively through review of the electronic medical records available at all the hospitals. Data confidentiality and patient anonymity were preserved.

Definition of outcomes

Postoperative complications were defined as any complication that led to direct intervention involving treatment (pneumothorax, invasive procedures, etc.) or resulted in biochemical and diagnostic changes (e.g., to renal failure or subcutaneous emphysema). Complications were identified through the analysis of electronic medical records, laboratory tests, and imaging examinations.

Postoperative mortality was defined as death that occurred within the first 30 days after surgery. The survival rate was calculated based on the period from the date of surgery to the date of the last medical contact.

Surgical resection (completeness of the resection) was defined as complete, incomplete, or uncertain according to the criteria established by the International Society for the Study of Lung Cancer.[9] In cases of segmentectomy, after removal of the specimen, routine analysis of the surgical margins was performed by frozen section biopsy.

Surgical technique

The first author participated in all the procedures, either as the surgeon operating the console or as the proctor. The surgical technique and treatment protocols were standardized and used in all cases. All patients underwent surgery with selective intubation confirmed by bronchoscopy. Although an epidural catheter for postoperative analgesia was used at the beginning of our study,[1] it is no longer utilized. Anesthesia was carried out before the incision for the first port and, after the introduction of the camera, the 4th to 11th intercostal spaces were blocked under direct vision. The robotic lobectomy technique we used was originally described by Dylewski et al.[10] and modified by our group.[1] The patient is placed in the supine position with armpit padding, and the robot is positioned close to the head of the patient. In total there are four ports: three for the robotic arms and one for the assistant surgeon.[1] The first incision is performed at the 7th or 8th intercostal space in the posterior axillary line and, with the aid of an endoscope, the locations for the other ports are selected.

During the postoperative period, patients are usually moved to the inpatient unit. Only elderly patients with multiple comorbidities or those who had any intraoperative complications are moved to the ICU. Postoperative analgesia includes oral dipyrone every 6 h, as well as anti-inflammatory drugs and gabapentin. We avoided the use of oral opioids as much as possible.

Statistical analysis

Continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR). The Shapiro-Wilk test was used for normality analysis. Categorical variables are expressed as absolute and relative frequencies. Survival rate analyses were performed by using the Kaplan-Meier method. The type I error threshold was set at 5%. Stata software, version 13 (StataCorp LP, College Station, TX, USA), was used for the statistical analyses.

RESULTS

We included 154 patients diagnosed with non-small cell lung cancer who underwent surgical resection by robotic surgery. The characteristics of the patients are described in Table 1. The mean age was 65.0 ± 9.5 years (range: 30-85 years). As can be seen in Table 2, the most common histological type was adenocarcinoma, in 126 patients (82%), followed by epidermoid carcinoma, in 14 (9%), and carcinoid tumors, in 14 (9%). Of the 154 patients in the sample, 109 (71%) presented stage I lung cancer. The most common type of surgery was lobectomy, in 133 patients (86.3%), followed by segmentectomy, in 21 (13.7%), as shown in Table 3. The mean overall operative time was 209 ± 80 min; being 214 ± 80 min for lobectomies and 167 ± 51 min for segmentectomies ($p = 0.01$). The mean number of resected lymph nodes was 12.0 ± 6.5 (range: 2-38), and the mean number of lymph node stations sampled was 6 ± 1 (range: 2-9). The pathological outcome and final staging are described in Table 4. There was no conversion to video-assisted thoracoscopic surgery or thoracotomy in any case, nor was there significant intraoperative bleeding.

Postoperative complications occurred in 32 patients (20.4%). Prolonged air leak was the most common

Table 1. Characteristics of the sample.[a]

Characteristic	(N = 154)
Gender	
Female	72 (46.5)
Male	82 (53.5)
Age, years	65 ± 9.5 (30-85)
BMI, kg/m^2	27.1 ± 4.9 (19.6-51.4)
Pulmonary function	
FEV_1, L/min	2.35 ± 0.74 (1.04-4.29)
FVC, % of predicted	87 ± 18 (40-125)
Comorbidities	
Smoking	91 (62)
Arterial hypertension	77 (54)
COPD	34 (24)
Previous neoplasia at another location	33 (23)
Heart failure	26 (18)
Diabetes mellitus	20 (14)
Kidney failure	6 (4)
Chronic liver disease	6 (4)

BMI: body mass index. [a]Values expressed as n (%) or mean ± SD (range).

Table 2. Histological types.

Histological type	(N = 154)
Adenocarcinoma in situ	7
Minimally invasive adenocarcinoma	11
Adenocarcinoma - predominantly lepidic	11
Adenocarcinoma - predominantly papillary	10
Adenocarcinoma - predominantly micropapillary	4
Adenocarcinoma - predominantly acinar	22
Adenocarcinoma - invasive mucinous pattern	6
Adenocarcinoma - enteral pattern	3
Adenocarcinoma - solid pattern	2
Invasive adenocarcinoma (subtype not reported)	49
Adenosquamous carcinoma	1
Typical carcinoid tumor	11
Atypical carcinoid tumor	3
Epidermoid carcinoma	14

complication, in 15 patients (9.5%), and 7 patients (4.4%) were discharged with a chest tube in place. In addition, 4 patients (2.5%) required pleural drainage after removal of the chest tube. Chylothorax occurred in 4 patients (2.5%). All were treated with dietary measures; however, 2 underwent reoperation for thoracic duct ligation due to persistent lymphatic fistula. One patient who underwent right upper lobectomy required reoperation due to torsion of the middle lobe, which was resected. Another patient had a severe anaphylactic reaction at the end of a segmentectomy, with subsequent cardiopulmonary arrest, which was promptly reversed, with no motor or neurological sequelae. Yet another patient presented trauma as a result of endotracheal intubation, leading to laryngeal edema and the need for tracheostomy during extubation. On postoperative day 7, she presented intestinal perforation due to Ogilvie's syndrome. Emergency laparotomy revealed a perforated cecum. A right hemicolectomy and temporary colostomy were performed. The patient showed no further complications in the postoperative period. The colostomy was reversed 2 months after hospital discharge. All of the complications are shown in Table 5.

The median length of hospital stay was 4 days (IQR: 3-6 days). The median pleural drainage time was 2 days (IQR: 2-4 days). Procedure-related death occurred in 1 patient (0.5%), 12 days after a lobectomy. That patient had developed pneumonia, sepsis, and multiple organ failure.

Pulmonary resection was categorized as complete in 97.4% of the cases. In 2.6% of patients, resection was categorized as uncertain due to the presence of at least one mediastinal lymph node affected by a neoplasm. Recurrence of neoplastic disease occurred in 11 patients (7.8%). The median overall survival and

Table 3. Types of surgical procedures performed.

Type of surgical procedure	(N = 154)
Lobectomy	133 (86.3%)
Upper right lobe	51
Upper right lobe + bronchoplasty	2
Middle lobe	5
Lower right lobe	28
Upper left lobe	21
Upper left lobe + bronchoplasty	1
Lower left lobe	24
Middle lobe + lower right lobe	1
Segmentectomy	21 (13.7%)
Upper right lobe	
Apical segment (S1)	1
Posterior segment (S2)	2
Anterior segment (S3)	1
Lower right lobe	
Upper segment (S6)	4
Basilar segments (S7 +S8 + S9 + S10)	1
Segment (S7 + S8)	1
Upper left lobe	
Apical-posterior segments + anterior (S1 + S2 + S3)	6
Lingular segment (S4 + S5)	1
Lingular segment (S4)	1
Lower left lobe	
Upper segment (S6)	2
Anterior basal segment (S8)	1

Table 4. Final pathological tumor-node-metastasis staging.

T	N	M	Stage	n	%
In situ	0	0		7	
1a(mi)	0	0	1A1	10	20.5
1a	0	0		15	
1b	0	0	1A2	41	26.0
1c	0	0	1A3	22	14.0
2a	0	0	IB	17	11.0
2b	0	0	IIA	6	4.0
1b	1	0		5	
1c	1	0	IIB	4	9.5
3	0	0		6	
1a	2	0		2	
1b	2	0	IIIA	4	11.5
2a	2	0		4	
2b	2	0		3	
3	1	0		3	
4	1	0		2	
3	2	0	IIIB	4	2.5
1c	0	1b	IVA	1	1.0
3	X	1[a]		1	

T: tumor; N: node; and M: metastasis.

median recurrence-free survival are shown in Figure 1. Among patients with recurrence of neoplastic disease, 2 (20%) had a confirmed tumor-node-metastasis (TNM) stage of N2. Disease recurrence occurred primarily in the pleura (35%), as well as through metastasis to the central nervous system (15%) and bones (10%). The mean follow-up period was 326 ± 274 days (range: 3-1,110 days). Two patients died due to the

progression of neoplastic disease. The overall mortality rate in the present cohort was 1.5%, corresponding to three deaths.

DISCUSSION

The present study portrays a consecutive series of 154 patients with primary lung cancer who were treated with pulmonary resection by robotic surgery. Our project started in 2015[1] and has seen a large increase in the number of individuals so treated since then. Most of the patients had stage I lung cancer. This predominance of early-stage tumors is in contrast with data collected for Brazil as a whole. According to the registry of malignant neoplasms in the state of São Paulo, only 1,835 (8.8%) of the 20,850 lung cancer patients registered between 2000 and 2010 had stage I disease.[11,12] That difference can be explained by the fact that our sample was composed of highly selected patients treated surgically at public and private referral hospitals, where they had greater access to chest CT scans and lung cancer screening programs.

The morbidity and mortality rates in the present study were 20.4% and 0.5%, respectively. These data are in line with those recently reported in the literature and represent the modern reality of thoracic surgery. This is a clear advance over the rates reported in studies previously conducted in Brazil. The analysis performed by Tsukazan et al.,[3] using the database of the Sociedade Brasileira de Cirurgia Torácica (SBCT, Brazilian Society of Thoracic Surgery), compared patients submitted to pulmonary resection by thoracotomy and those submitted to pulmonary resection by video-assisted thoracoscopic surgery. The complication rate in the thoracotomy group was 30.1%, compared with 21.8% in the video-assisted thoracoscopic surgery group. Regarding the mortality rate, it was 2.5% in the thoracotomy group and 1.6% in the video-assisted thoracoscopic surgery group. Another study using the SBCT database, which included pulmonary resections by video-assisted thoracoscopic surgery, reported a surgical morbidity rate of 19.1% and a mortality rate of 2.0%.[2] In our study, morbidity is comparable to that in patients who underwent video-assisted thoracoscopic surgery. However, there was a significant reduction

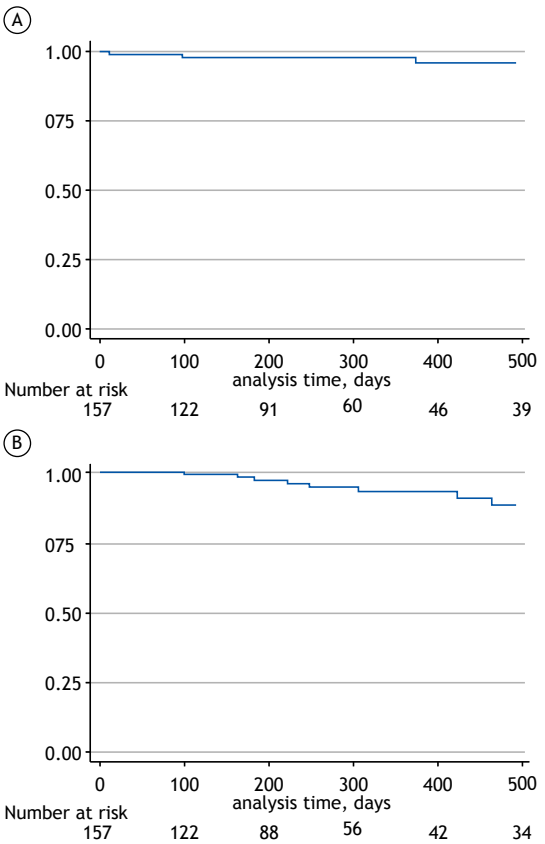

Figure 1. Kaplan-Meier curves. In A, the overall survival curve. In B, the disease-free survival curve.

Table 5. Complications.[a]

Complication	n = 32 (20.4)
Prolonged air leak	15 (9.5)
Discharge with pleural drainage	7 (4.4)
Pneumothorax + further pleural drainage	4 (2.5)
Pulmonary embolism	4 (2.5)
Chylothorax	4 (2.5)
Pneumonia	3 (1.8)
Reoperation	3 (1.8)
Cardiac arrhythmia	2 (1.2)
Tracheostomy	2 (1.2)
Urinary tract infection	2 (1.2)
Non-dialysis dependent renal insufficiency	2 (1.2)
Dialysis dependent renal insufficiency	1 (0.6)
Endotracheal intubation trauma: glottic edema	1 (0.6)
Intestinal subocclusion	1 (0.6)
Intestinal perforation + colostomy	1 (0.6)
Hospital readmissions within 90 days	12 (7.5)

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

in postoperative mortality (1.6-2.0% vs. 0.5%). This is corroborated by other studies of robotic pulmonary resections, which reported mortality rates of 0.2-1.3% and morbidity rates of 34.6-43.8%.[5-7]

Prolonged air leak was the most common complication in our sample. In fact, this finding is similar to that reported by other investigators.[5-7,13] Air leak prolongs the length of hospital stay, increases the chance of pleural infection, and often leads to additional procedures such as chest tube insertion. In our study, 4 patients (2.5%) required extended pleural drainage. In addition to the inconveniences associated with prolonged pleural drainage, prolonged hospitalization greatly increases hospital costs and decreases the cost-effectiveness of the robotic procedure.[14]

Although overall morbidity was in line with the most recent data, the profile of complications in our sample was different from that reported in other studies. Severe cardiovascular events occurred in only 3 patients. One patient had atrial fibrillation, which was treated with medications; another had myocardial ischemia and was treated with percutaneous coronary stenting; the third developed a severe anaphylactic reaction at the end of a segmentectomy, with subsequent cardiopulmonary arrest. Nasir et al.[15] observed arrhythmia in 7% of patients who underwent pulmonary resection, a complication that was not observed in our sample. However, postoperative chylothorax was observed in 4 patients (2.5%). We believe this is related to extensive lymph node dissection in the right paratracheal stations. These findings are confirmed in a study by Bryant et al.,[16] who demonstrated that lobectomy ($p = 0.011$), robotic surgery ($p = 0.032$) and the N2 pathological stage ($p = 0.027$) are predictors of chylothorax occurrence. Therefore, we currently recommend the use of clips in this region and initial aspiration of the pleural space at -8 cmH_2O in the postoperative digital drainage system.

The survival rate curve for patients treated surgically in this study is above 90% at 2 years, which is consistent with data in the literature.[4-7] However, because of the short follow-up period, it was not possible to calculate the median survival rate in our sample. With a longer follow-up period, we would be able to analyze the impact of sublobar resections among patients treated surgically, specifically in relation to the local recurrence rate. The rate of complete resection in the present study (97.4%) is also consistent with data in the literature.[13,17]

Few studies have drawn direct comparisons between video-assisted thoracoscopic surgery and robotic surgery. However, there is evidence that robotic surgery is superior to traditional video-assisted thoracoscopic surgery.[5,7,8,14,15] The former provides reductions in morbidity and especially operative mortality. In addition, the extent of the lymph node disease/dissection, and the resulting mediastinal upstaging, make robotic surgery more attractive in cases of locally advanced disease.[17] In the case of occult N2 disease, robotic surgery can also reduce recovery time and the time between surgery and adjunctive treatment, thereby making it more likely that full doses of systemic therapeutic agents will be administered to patients.[17]

We conclude that robotic pulmonary resection is safe for the treatment of lung cancer, and the initial experience in Brazil is comparable to that reported in studies conducted elsewhere. Certainly, the method and its indications will be consolidated over time.

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ORIGINAL ARTICLE

Sedation for bronchoscopy: current practices in Latin America

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ABSTRACT

Objective: To evaluate current practices in sedation for bronchoscopy in Latin America. **Methods:** This was an anonymous survey of select members of the Latin American Thoracic Association. The questionnaire, made available online from November of 2015 through February of 2016, was designed to collect data on demographic characteristics; type of facility (public or private); type/volume of bronchoscopies; type of sedation; and type of professional administering the sedation. **Results:** We received 338 completed questionnaires from 19 countries; 250 respondents (74.0%) were male. The mean respondent age was 36.0 ± 10.5 years. Of the 338 respondents, 304 (89.9%) were pulmonologists; 169 (50.0%) worked at public facilities; and 152 (45.0%) worked at teaching facilities. All of the respondents performed diagnostic fiberoptic bronchoscopy, 206 (60.9%) performed therapeutic fiberoptic bronchoscopy, 125 (37.0%) performed rigid bronchoscopy, 37 (10.9%) performed endobronchial ultrasound, and 3 (0.9%) performed laser therapy/thermoplasty/cryotherapy. Sedation for bronchoscopy was employed by 324 respondents (95.6%). Of the 338 respondents, 103 (30.5%) and 96 (28.4%) stated, respectively, that such sedation should "usually" and "never" be administered by a bronchoscopist; 324 (95.9%) supported training bronchoscopists in sedation. Sedation administered by a bronchoscopist was reported by 113 respondents, conscious sedation being employed by 109 (96.2%). The use of benzodiazepines, propofol, and opiates was reported, respectively, by 252 (74.6%), 179 (52.9%), and 132 (39.0%) of the 338 respondents. Deep sedation and general anesthesia were more common at private facilities. **Conclusions:** The consensus seems to be that a well-trained bronchoscopist can safely administer sedation for bronchoscopy. However, approximately 40% of bronchoscopists do not do so regularly.

Keywords: Bronchoscopy/methods; Conscious sedation/statistics & numerical data; Hypnotics and sedatives.

INTRODUCTION

Bronchoscopy is an invasive technique that causes discomfort and is difficult for many patients to tolerate.[1,2] Because of the increase in the number, types, and duration of diagnostic/therapeutic endoscopic procedures, together with the shift in societal attitudes regarding pain and discomfort during invasive procedures, the use of sedation in endoscopy is becoming more common. Guidelines recommend offering sedation to all patients undergoing bronchoscopy, except when there are contraindications,[1,2] to improve the tolerance and yield of the procedure. Nevertheless, many endoscopy teams currently perform most of their procedures without sedation. Sedation practices vary not only among countries but also among hospitals and even among bronchoscopists at individual hospitals.[3-6]

We set out to study the current sedation practices for bronchoscopy in Latin America. To that end, we made an online questionnaire available to the members of the *Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Association). The ALAT is a scientific society for health care professionals in Latin America with a common interest in respiratory maladies. When the questionnaire was made available (in November of 2015), the ALAT had 3,069 members, 481 of whom belonged to the Respiratory Endoscopy Section (ALAT-Endoscopy).

METHODS

The questionnaire consisted of 29 questions, most of which were closed-ended, multiple-choice questions. It was made available to ALAT-Endoscopy members via Google Forms, a web-based survey tool. The form was provided in Spanish (http://goo.gl/forms/2n72A7agJo) and in Portuguese (http://goo.gl/forms/tF6rEIIYQZ). The time estimated for its completion was 5-7 min. The links to the questionnaire and the accompanying e-mails were sent by the ALAT secretary, on behalf of the investigators and ALAT-Endoscopy, to the 481 ALAT-Endoscopy members. Five e-mails were sent to each potential respondent: two initially informing them of the project and inviting them to participate; and three serving as reminders and announcing its closing.

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Respondents were asked to provide data on demographic characteristics; the type of facility (public or private); the type and volume of the bronchoscopies performed; the type of sedation; and the type of professional administering the sedation. The questionnaire also comprised questions regarding the views of the respondents on sedation and on training bronchoscopists in sedation; regarding the techniques employed; regarding interventionism; and regarding the characteristics of the bronchoscopies performed, in the operating room and in the ICU. Respondents were also asked about their training in advanced life support and airway management. We defined sedation as any pharmacological intervention aimed at reducing the level of awareness and anxiety of the patient, to improve the tolerability of the procedure. The questions were based on those employed in previous, similar studies[3,5-7] and on the experience of the investigators. The questionnaires were completed anonymously and voluntarily between 1 November 2015 and 1 March 2016.

RESULTS

Of a total of 354 questionnaires received, 16 were excluded: 15 because they were duplicates; and 1 because it had been completed by a nurse rather than by a physician. We did not exclude any questionnaires for being incomplete, although 12 had one unanswered question and 1 had two unanswered questions (none of the unanswered questions being about sedation). We analyzed 338 surveys, corresponding to 70.3% of the 481 ALAT-Endoscopy members contacted.

Of the 338 respondents, 250 (74.0%) were male and 174 (51.4%) were under 45 years of age (Table 1). A total of 19 countries were represented (Figure 1).

The number of bronchoscopies and the size of the facility (number of beds) were directly related: 128 (37.9%) of the respondents reported that the number of bronchoscopies/year at their facilities was < 100, 105 (31.1%) reported that number to be 100-300, 51 (15.1%) reported it to be 300-600, and 54 (16.0%) reported it to be > 600. Of the 338 respondents, 152 (45.0%) worked at medical centers with resident training programs, which were also the facilities where a higher volume of bronchoscopies were performed and a broader range of techniques were employed.

All of the specialists surveyed reported that diagnostic fiberoptic bronchoscopy was the primary procedure performed. Therapeutic fiberoptic bronchoscopy was the second most common procedure, performed by 206 (60.9%) of the respondents, followed by rigid bronchoscopy, performed by 125 (37.0%); radial endobronchial ultrasound, performed by 17 (5.0%); linear endobronchial ultrasound, performed by 20 (5.9%); and laser therapy, thermoplasty, or cryotherapy, performed by 3 (0.9%). The sample collection techniques employed most frequently in the last year were bronchoalveolar lavage, employed by 331 (97.9%) of the respondents, bronchial brushing, employed by 303 (89.6%), transbronchial lung biopsy, employed by 294 (87.0%), and transbronchial needle aspiration, employed by 108 (32.0%). Of the 338 respondents, 214 (63.3%) reported that the specialist in charge opted to introduce the bronchoscope nasally, 70 (20.7%) reported that it was introduced orally, and 32 (9.5%) reported that it was introduced through a laryngeal mask; 12 (3.6%) reported that endotracheal intubation was used.

We explored the perceptions of bronchoscopists regarding sedation. Of the 338 respondents, 211 (62.5%) stated that they believed sedation was "always" necessary during bronchoscopies, whereas 120 (35.5%) stated that it was "occasionally" necessary and 7 (2.1%) stated that it was "never" necessary (Figure 2).

As illustrated in Figure 3, sedation was used in all bronchoscopies by 14 (4.1%) of the respondents, whereas it was not used in any of the bronchoscopies performed by another 14 (4.1%). On the question about how often bronchoscopies were performed under sedation at the respective medical centers, 211 (62.5%) of the respondents answered "regularly", 69 (20.5%) answered "occasionally", 44 (13.0%) answered "rarely", and 14 (4.1%) answered "never" (Figure 4).

Of the 324 specialists who reported that sedation was employed for bronchoscopy (Figure 5), 186 (57.4%) reported that it was administered by an anesthetist, 113 (34.9%) reported that it was administered by a bronchoscopist, and 25 (7.7%) reported that it was sometimes administered by an anesthetist and sometimes administered by a bronchoscopist. Of the 338 respondents in the sample as a whole, 103 (30.5%) were of the opinion that sedation for bronchoscopy should "always" or "usually" be administered by a bronchoscopist, whereas 96 (28.4%) believed that the bronchoscopist should "never" administer it. The remaining 140 (41.4%) believed that bronchoscopists should "sometimes" perform this task. When a bronchoscopist performed the sedation, it was almost always conscious sedation, which was commonly employed by 109 (96.2%) of the 113 bronchoscopists who administered sedation for bronchoscopy. Only 11 (3.2%) of the 338 respondents reported using deep sedation. The most commonly used drugs were benzodiazepines, which were administered by 242 (74.6%) of the 324 specialists who reported that sedation was employed for bronchoscopy, followed by propofol, administered by 171 (52.9%), opiates, administered by 126 (39.0%), and ketamine, administered by 11 (3.5%). Sedation performed by a bronchoscopist is considered safe, our respondents giving it a mean safety rating of 3.8 ± 1.2 out of 5.0 (95% CI: 3.7-3.9; median, 4). Of the 338 respondents, 227 (67.2%) indicated that sedation performed by bronchoscopists is quite safe or safe, whereas 17 (5.0%) indicated that it is not safe at all, and 324 (95.9%) expressed their support for ALAT-sponsored programs of training in sedation for bronchoscopists.

Table 1. Characteristics of the respondents and their medical centers. Latin American Thoracic Association survey, 2016.

Characteristic	(N = 338)
Gender, n (%)	
Male	250 (73.4)
Female	88 (26.0)
Age (years), mean ± SD (range)	47.0 ± 10.5 (28-75)
Age group, n (%)	
< 45 years	164 (51.4)
≥ 45 years	174 (48.6)
Specialty, n (%)	
Pulmonology	304 (89.9)
Thoracic surgery	21 (6.1)
Other	13 (3.8)
Recent training (last 5 years), n (%)	
Airway management	215 (63.6)
Advanced life support	223 (65.9)
Type of medical center, n (%)	
Public	169 (50.0)
Private	112 (33.1)
Mixed (public and private)	57 (16.9)
Size of the medical center, n (%)	
< 100 beds	84 (24.9)
100-300 beds	124 (36.8)
301-500 beds	70 (20.8)
> 500 beds	59 (17.5)

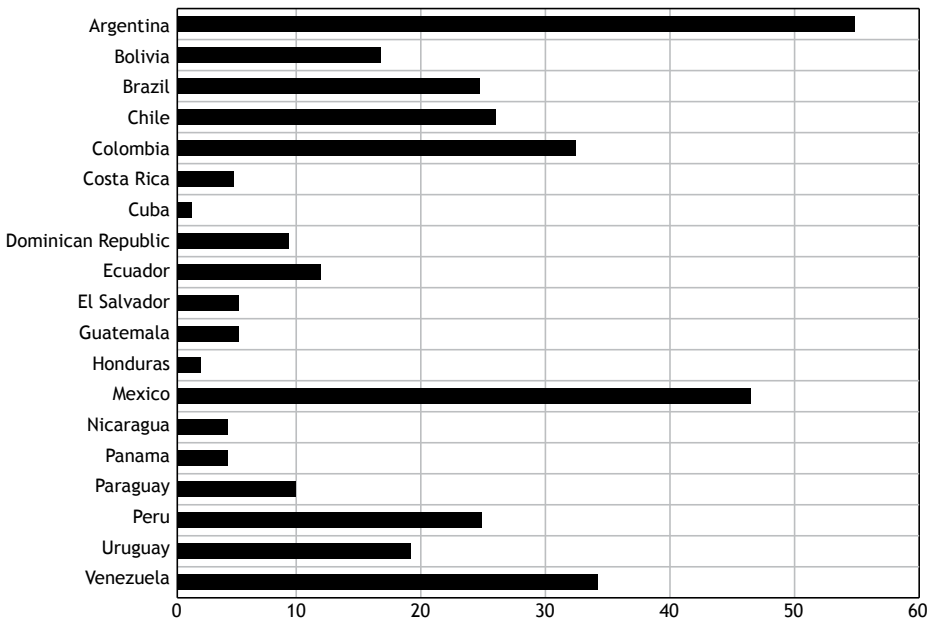

Figure 1. Current countries of residence of the respondents at the time of the 2016 survey of members of the Respiratory Endoscopy Section of the Latin American Thoracic Association.

The male respondents were older than were their female counterparts, with no differences among the medical centers surveyed. Multivariate analysis showed no significant differences between the male and female respondents in terms of the proportion who believed that bronchoscopy should always be performed under sedation (60.2% vs. 63.2%; p = 1.00) and that of those who believed that bronchoscopists should always receive specific training to perform sedation (47.1% vs. 42.3%; p = 0.429).

The study sample was divided into two groups by the age of the respondents: < 45 years of age (n = 164);

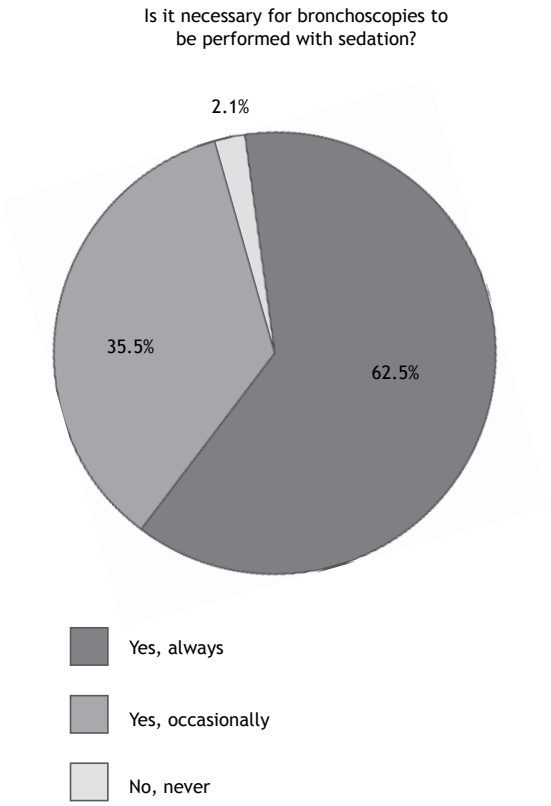

Figure 2. Proportional distribution of the responses regarding the need for sedation during bronchoscopy. 2016 survey of members of the Respiratory Endoscopy Section of the Latin American Thoracic Association.

and ≥ 45 years of age (n = 174). Among those ≥ 45 years of age, there were greater proportions of males, of specialists who worked in medical centers with fewer beds, and of specialists who worked at medical centers with no resident training. The proportion of respondents who believed that bronchoscopies should be performed without sedation was also higher in the ≥ 45-year age group (3.4% vs. 0.6%; p = 0.032), as was that of those reporting that an anesthetist was in charge of administering sedation for bronchoscopy (60.6% vs. 54.3%; p = 0.04). Of the bronchoscopists in the < 45-year and ≥ 45-year age groups, 66.3% and 68.4%, respectively, considered sedation performed by a bronchoscopist to be "safe" or "quite safe" (p = 0.546). In the latter group, the proportion of those who reported administering opiates was significantly higher (47.0% vs. 31.5%; p = 0.004), whereas that of those who reported using protected catheter techniques (for cytology or microbiology) was significantly lower (24.0% vs. 44.4%; p = 0.0001).

We found that the private medical centers had fewer beds than did the public medical centers. The proportion of male respondents was higher for the private medical centers. The respondents for the private medical centers were also older than were the respondents for the public medical centers. Resident training was reportedly less common at private medical centers than at public medical centers. The opinion that sedation should always be used for bronchoscopy was equally common among the respondents working at private medical centers and those working at public medical centers (69.7% and 60.7%, respectively; p = 0.355),

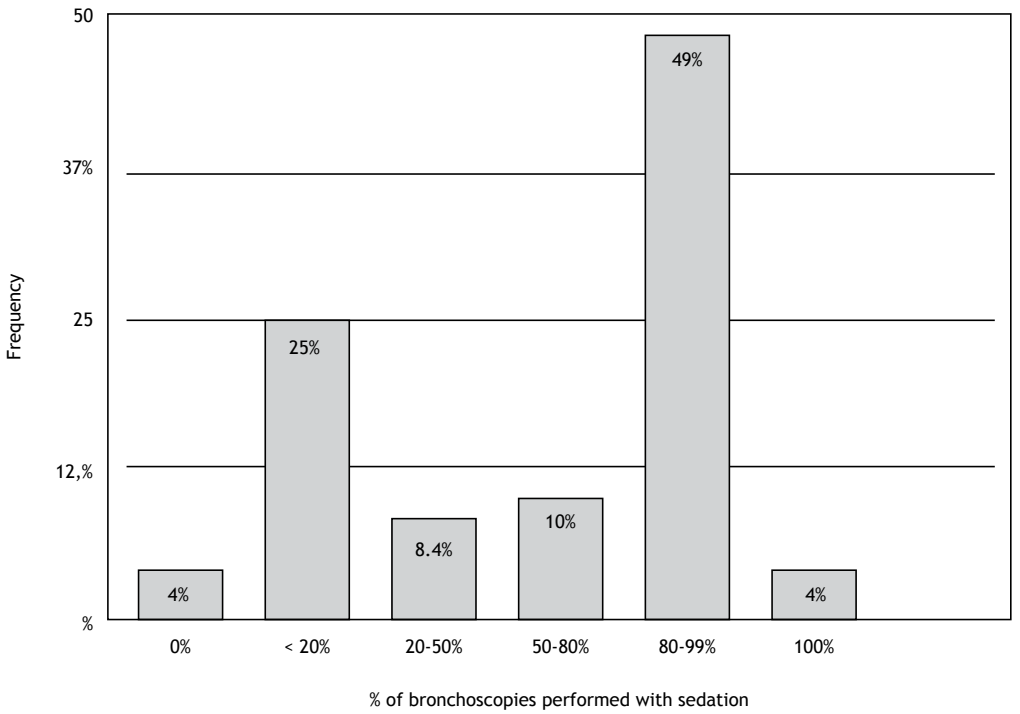

Figure 3. Proportions of bronchoscopies performed with sedation. 2016 survey of members of the Respiratory Endoscopy Section of the Latin American Thoracic Association.

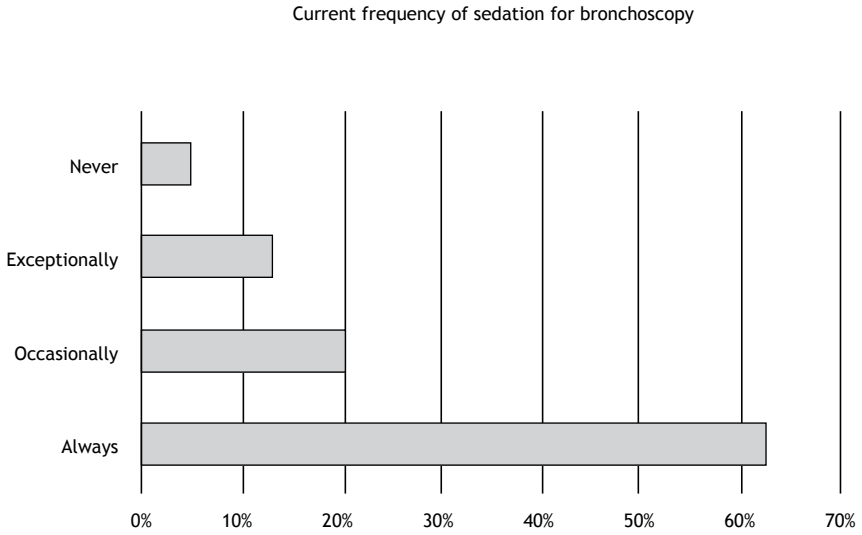

Figure 4. Current frequency of sedation for bronchoscopy. 2016 survey of members of the Respiratory Endoscopy Section of the Latin American Thoracic Association.

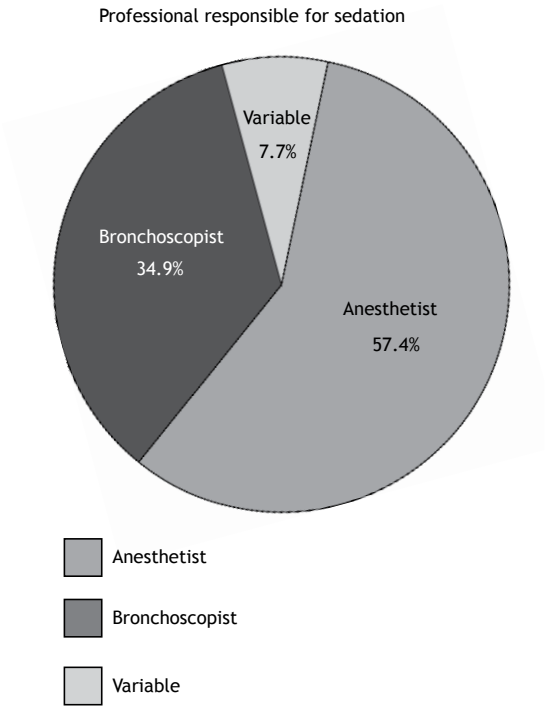

Figure 5. Professional responsible for administering sedation for bronchoscopy. 2016 survey of members of the Respiratory Endoscopy Section of the Latin American Thoracic Association.

as was the response that it was used on a regular basis (64.6% and 60.9%, respectively; $p < 0.05$). The proportion of respondents working at facilities at which an anesthetist was responsible for administering the sedation was higher among those working at private medical centers (69.2% vs. 52.5%; $p = 0.001$), as was that of those working at medical centers at which bronchoscopists performed deep sedation (6.5% vs. 0.7%; $p = 0.003$). In addition, benzodiazepine use was reported by fewer respondents working at private medical centers than respondents working at public medical centers (64.6% vs. 79.9%; $p = 0.006$), as was opiate use (24.8% vs. 46.6%; $p < 0.001$), although propofol use was comparable (59.3% and 50.0%, respectively; $p < 0.05$).

DISCUSSION

The number of endoscopic procedures and of the sedation practices associated therewith has grown exponentially in recent years.[8] The questionnaire employed in this survey was designed to obtain information on current practices in sedation for bronchoscopy, and well as on the general characteristics of bronchoscopy procedures performed in Latin America.

Most of our participants were male, were pulmonologists, and were based in South American countries, although a considerable number of respondents were working at medical centers in Mexico. Each region can have its sphere of influence and influencer. For example, bronchoscopists in Australia and New Zealand who were trained in the United Kingdom perform bronchoscopies from the front of the patient rather than from the back.[6]

Although most (62.5%) of our respondents held the opinion that sedation is always necessary during fiberoptic bronchoscopy, a subanalysis showed that the proportion of respondents who believed that such sedation is not required was higher among those who were ≥ 45 years of age. For this variable, we found no significant differences between genders or between private and public medical centers. Nevertheless, 4% of respondents stated that bronchoscopies are performed without sedation at their facilities, again with no significant difference between private and public medical centers.

At most of the medical centers surveyed in the present study, especially the private ones, an anesthetist was in charge of sedation for bronchoscopy and its monitoring. In 2012, Tozkoparan et al.[5] surveyed bronchoscopists in Turkey. The authors found that 36% of bronchoscopies were performed without sedation, that propofol was used in 21%, and that midazolam was used in 78%. They also identified differences among thoracic surgeons, anesthetists, and pulmonologists: anesthetists favored the use of propofol, whereas thoracic surgeons were the ones least likely to sedate their patients for bronchoscopy. The previously cited survey of bronchoscopy practices in Australia and New Zealand, conducted in 2013 by Barnett et al.,[6] produced similar results: 6% of bronchoscopies were performed without sedation; sedation was administered by an anesthetist at 81% of the private medical centers, compared with 38% of the public medical centers. The authors also found that 94% of the bronchoscopies involved the use of a two-sedative combination, the midazolam-fentanyl combination being the sedative of choice in 96% of the cases in which sedation was administered by a bronchoscopist and in 53% of those in which it was administered by an anesthetist, whereas propofol was used less commonly (in 4% and 55%, respectively). That same study showed that bronchoscopists administered the sedation in 45% of the procedures performed at public medical centers and in 19% of those performed at private medical centers.

In the present survey, ALAT-Endoscopy members reported performing bronchoscopies mainly in patients under conscious sedation, benzodiazepines being the drug of choice. These data are similar to those reported for countries outside Latin America, where there are also differences of opinion regarding whether or not bronchoscopy patients should be offered sedation, regarding the optimal type of sedation, and regarding the drugs that are the most appropriate.[4,9-12] In a study conducted in Italy in 2008, Facciolongo et al.[3] reported that 13.8% of bronchoscopists always administered sedation, 24.4% administered it frequently (in > 80% of bronchoscopies), and 60% administered it occasionally (in < 20% of bronchoscopies), the sedatives most often employed being midazolam and diazepam (in 70.7% and 23.6% of bronchoscopies, respectively). In a study conducted in 2010, Ni et al. reported that, in Taiwan, bronchoscopies were mainly performed with local anesthesia only.[13] The choice between conscious sedation and deep sedation seems to be an important one, given that deep sedation has been shown to be more cost-efficient for endobronchial ultrasound-guided transbronchial needle aspiration,[14] the use of which was reported by 32% of the respondents in the present survey.

Sedation performed by a bronchoscopist was deemed "safe" or "quite safe" by approximately two thirds of the ALAT members surveyed in our study. Approximately, one third of the respondents believed that the bronchoscopist should "always" or "almost always" be in charge of the sedation and another one third thought that the bronchoscopist should "never" administer the sedation. There was a consensus regarding the need for bronchoscopists to be trained in the use of sedation, which is significant because only approximately half of the questionnaires came from medical centers with resident training programs.

The results of the present survey reveal that, despite the advances in sedation techniques, drugs, and monitoring, there are still medical centers in Latin America where bronchoscopies are performed without sedation. That could be due to a lack of resources (human or material) or to medical idiosyncrasies. The fact that the proportion of physicians who believed that bronchoscopy does not require sedation was greater among those ≥ 45 years of age could be explained by a lack of experience with drugs used for short duration procedures, such as propofol,[9,15,16] remifentanil,[17,18] and dexmedetomidine,[19,20] which have been introduced relatively recently. The difference between younger and older physicians could also be a result of the fact that respiratory medicine training a few decades back was more focused on tuberculosis, whereas residents in respiratory medicine now receive training that focuses more on critical care.[21]

Switching the bronchoscopy procedure from the operating room to the endoscopy room is cost effective and does not sacrifice safety or patient satisfaction.[22,23] In addition, the development of a consensus in support of sedation being administered by non-anesthetists, in various scenarios,[24-28] paves the way for bronchoscopists to learn, practice, and take charge of patient sedation.[29,30]

Because propofol has a narrow therapeutic window,[28] most guidelines have recommended that it be administered only by specially trained professionals.[1,2] The use of propofol in bronchoscopy has been gaining ground: in 2002, it was not used at all in the United Kingdom[31]; and in 2010, it was used in only 4.1% of cases in Japan.[32] The previous controversy regarding the administration of propofol by non-anesthetists was mainly motivated by the fact that propofol has no antidote, by a fear of inducing sedation that is more profound than intended, and by the consequent risk to the patient.[28,33] The debate is over, and there are now numerous guidelines on and studies demonstrating the safety of sedation by non-anesthetists in digestive and respiratory endoscopy.[9-12,25,34-36] A number of studies have also shown that, for bronchoscopy, it is safe for nurses to administer propofol under the supervision of an endoscopist.[34,36] A clinical trial comparing propofol and midazolam for use in bronchoscopy showed that, with the appropriate training, non-anesthetists can safely administer propofol in outpatient settings.[35]

It is fundamental that non-anesthetists be qualified to manage any complications that may arise,[24,29,30,36-38] particularly in the respiratory tract.[38] The overwhelming majority of the respondents to this survey expressed their support for an ALAT-sponsored training program in sedation for bronchoscopy.

This study has some limitations. There are inherent methodological limitations to the use of questionnaires, including a possible memory bias and issues relating to the veracity of the data collected.[39] In addition, because we employed non-probability sampling, the number of participants per region or type of medical center might not be representative of that population. Furthermore, the survey was made available only to ALAT-Endoscopy members. It is likely that not all bronchoscopists in Latin America belong to ALAT, and those that do might not all belong to ALAT-Endoscopy. Moreover, participation was voluntary and not all members of ALAT-Endoscopy opted to participate. The fact that we did not get 100% participation might be due to a lack of interest or to difficulties in accessing the survey. However, the questionnaire was available online for four months and we sent several reminder e-mails. That four-month period and the multiple attempts to contact potential respondents, to improve the rate of participation, is standard in similar surveys.[40] By sending five reminder e-mails, we achieved a response rate of 70.3%, considerably higher than the 31% rate achieved in the study conducted in Australia and New Zealand,[6] in which only two reminder e-mails were sent. Another potential limitation is that we evaluated information provided by all participating bronchoscopists, rather than by hospital administrators or representatives. Therefore, the number of bronchoscopists might not have been equal to the number of medical centers. We also aimed to characterize the clinical practice of the individual bronchoscopists, rather than that of the medical centers. The information available might not be objective for several questions (number of beds, number of procedures, etc.), and some answers might not have been based on data. Other questions solicited opinions, which can be influenced by the work environment, personal experiences, etc. Health care systems and scenarios vary significantly, not only among Latin American countries but also among regions and cities within each country. Despite these limitations, we consider our results relevant to improving understanding of the current practices in sedation for bronchoscopy in Latin America, because we have shown that sedation for bronchoscopy is administered at many medical centers in Latin America, as well as that, although it is mainly administered by anesthetists, it is administered by the bronchoscopists themselves in a sizeable proportion of cases, and that bronchoscopy under sedation administered by a bronchoscopist is perceived (by other bronchoscopists) as being a safe technique if the bronchoscopist has been adequately trained.

Our findings show that, in Latin America, there is still a relatively high proportion of bronchoscopists (nearly 40%) who use sedation only occasionally or never. Given the intrinsic peculiarities of each region, it is essential for scientific communities and investigators, including those in Latin America, to generate scientific evidence of their own, to make region-specific recommendations regarding sedation for bronchoscopy, and to develop appropriate training programs for the professionals involved.

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Assessment of religious coping in patients with COPD

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Study carried out at the Hospital Universitário Walter Cantídio, Universidade Federal do Ceará, and at the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza (CE) Brasil.

ABSTRACT

Objective: To compare religious coping (RC) in patients with COPD and healthy individuals, as well as to determine whether RC is associated with demographic characteristics, quality of life, depression, and disease severity in the patients with COPD. **Methods:** This was a cross-sectional study conducted between 2014 and 2016, involving outpatients with moderate to severe COPD seen at one of two hospitals in Fortaleza, Brazil, as well as gender- and age-matched healthy controls. The Brief RCOPE scale assessed RC in all of the participants. We also evaluated the COPD group patients regarding symptoms, quality of life, and depression, as well as submitting them to spirometry and a six-minute walk test. **Results:** A total of 100 patients were evaluated. The mean age was 67.3 ± 6.8 years, and 54% were men. In the COPD group, the mean positive RC score was significantly higher than was the mean negative RC score (27.17 ± 1.60 vs. 8.21 ± 2.12; p = 0.001). The mean positive RC score was significantly higher in women than in men (27.5 ± 1.1 vs. 26.8 ± 2.8; p = 0.02). Negative RC scores were significantly higher in the COPD group than in the control group (p = 0.01). Negative RC showed an inverse association with six-minute walk distance (6MWD; r = −0.3; p < 0.05) and a direct association with depressive symptoms (r = 0.2; p < 0.03). Positive RC correlated with none of the variables studied. Multiple regression analysis showed that negative RC was associated with 6MWD (coefficient = −0.009; 95% CI: −0.01 to −0.003). 6MWD explained the variance in negative RC in a linear fashion. **Conclusions:** Patients with COPD employ negative RC more often than do healthy individuals. Exercise capacity and depressive symptoms are associated with negative RC.

Keywords: Religion; Spirituality; Adaptation, psychological; Quality of life; Pulmonary disease, chronic obstructive.

INTRODUCTION

COPD is a preventable and treatable disease characterized by airflow limitation and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. COPD is currently considered the fourth leading cause of death worldwide.[1,2]

The systemic inflammatory component of COPD can trigger or worsen comorbidities, such as diabetes mellitus, metabolic syndrome, obstructive sleep apnea, and cachexia due to loss of lean body mass.[3] The main symptoms of COPD are dyspnea, cough, exercise intolerance, worsening of nutritional status, and increased levels of anxiety and depression.[4]

The severity of COPD and the difficulties in coping with the limitations imposed by the disease, as well as the consequent prospect of near death, may lead to varying degrees of impairment in patient quality of life (QoL).[5]

In this context, religiosity and spirituality can be considered coping strategies in chronic diseases. Religiosity is defined as the use of faith-related beliefs, values, practices, and individual rituals, whereas spirituality is more subjective and permeates questions about the meaning of life.[6]

Worldwide, the term religious coping (RC) is recognized as referring to behaviors adopted by the individual in order to cope with a stressful condition. RC can be perceived as having positive and negative aspects. Positive RC refers to benevolent religious appraisals and religious forgiveness, reflecting a secure relationship with God. In contrast, negative RC refers to reappraising God's powers or feeling abandoned or punished by God, reflecting a tenuous relationship with God.[7]

To date, however, few studies have addressed RC strategies in patients with COPD. RC strategies have been studied in other chronic diseases, such as cancer, chronic kidney disease, and inflammatory bowel disease,[8] with the practice of religiosity and spirituality being found to be associated with better health status and well-being.[9,10] In patients with advanced lung disease, studies indicate that RC is associated with higher levels of social functioning, but they also indicate that it is associated with greater psychological distress and disability.[11,12]

Following this line of reasoning, it is very important that RC be assessed because it is how individuals deal with physically and mentally stressful situations from the perspective of their health status, and because RC

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strategies can be an integral part of patient management and treatment.

The objectives of the present study were to compare RC in patients with COPD and healthy individuals, as well as to determine whether RC is associated with demographic characteristics, quality of life measures, depression, and disease severity as defined by pulmonary function and functional exercise capacity, in the patients with COPD.

METHODS

This was a cross-sectional study conducted at the pulmonology outpatient clinics of the Federal University of Ceará Walter Cantídio University Hospital and the Dr. Carlos Alberto Studart Gomes Messejana Hospital, both of which are located in the city of Fortaleza, Brazil, between February 2014 and February 2016. The study was conducted in accordance with Brazilian National Health Council Resolution 196/96, which sets out the ethical principles for human research, and was approved by the Research Ethics Committees of the Federal University of Ceará and the Dr. Carlos Alberto Studart Gomes Messejana Hospital (Ruling no. 855.310 and Ruling no. 901.995, respectively).

We consecutively selected patients who had a confirmed diagnosis of moderate to severe COPD, on the basis of spirometry results, as defined by the Global Initiative for Chronic Obstructive Lung Disease[1]; were between 40 and 80 years of age; and were clinically stable (no episodes of hospitalization for COPD exacerbation or infection in the three months prior to the study period). The exclusion criterion was the presence of other non-lung diseases that are considered disabling, severe, or difficult to control. Individuals for the control group were recruited from the community and, after agreeing to participate in the study, were sent to a room next to the outpatient clinic for administration of the Brief RCOPE scale.[13] The two groups (patients and controls) were matched for gender and age. The patients with COPD were evaluated for RC, quality of life, depression, pulmonary function, and exercise capacity.

RC was assessed by administering the Brief RCOPE scale,[13] which is considered a valid and reproducible instrument. This scale consists of 14 items that analyze positive aspects (7 items) and negative aspects (7 items) of RC, measured on a four-point Likert scale ranging from 1 (never) to 4 (nearly always). Scores for positive RC and negative RC can range from 7 to 28.[13] Scores close to 7 denote less use of RC, whereas scores close to 28 indicate greater use of RC.

Health-related QoL was assessed by using three different instruments, all of which have been validated for use in Brazil. The COPD Assessment Test is an instrument specifically designed for patients with COPD, consisting of eight questions addressing the impact of COPD symptoms, and its total score ranges from 0 (least severe impact) to 40 (most severe impact).[14] The Medical Outcomes Study 36-item Short-Form Health Survey[15] is a generic instrument consisting of 36 items that cover 8 domains: functional capacity; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health. These domains can be grouped into a physical component summary and a mental component summary. The physical and mental component summary scores can range from 0 to 100, with higher scores indicating better general health status. The Saint George's Respiratory Questionnaire[16] is designed specifically for individuals with respiratory disease and addresses aspects related to three domains affected by the disease—symptoms, activity, and psychosocial impact. Each domain has a maximum possible score; domain scores are calculated by summing up all the scores of the individual items in each domain, and the total is expressed as a percentage (0-100%) of the maximum possible score for that domain; higher scores indicate poorer QoL.[16]

Depressive symptoms were assessed by administering the Patient Health Questionnaire-9,[17] which consists of 9 items scored from 0 to 3 based on the frequency of occurrence of the complaint. The total score, which is the sum of all the scores of the individual items, indicates the following: no depression (0-4 points); mild depression (5-9 points); moderate depression (10-14 points); moderately severe depression (15-19 points); and severe depression (20 or more points).

Pulmonary function was assessed by spirometry, in accordance with Brazilian guidelines,[18] and FEV_1 and FVC were measured. The results obtained were expressed as a percentage of predicted values, on the basis of Brazilian population reference values.[19]

Exercise capacity was measured with the six-minute walk test, conducted in accordance with the European Respiratory Society/American Thoracic Society guidelines.[20] The patient was encouraged to walk as far as possible, in six minutes, on a 30-m level corridor. At the end of the test, the examiner recorded the total distance covered in six minutes, that is, the six-minute walk distance (6MWD).

Data were analyzed with SPSS Statistics software, version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive analysis was performed by calculating absolute frequencies, relative frequencies, means and standard deviations, or medians and interquartile ranges (IQRs). Normally distributed numerical variables were compared by using the Student's t-test for independent samples. Non-normally distributed numerical variables were compared by using the Mann-Whitney U test. Categorical variables were compared by using the Chi-square test. Correlations between numerical variables were analyzed with Pearson's correlation coefficient. Multivariate linear regression analysis was performed to identify factors potentially related to RC, and independent variables included in the multivariate model were those with a significance level < 5% in the univariate analysis. Statistical significance was set at $p < 0.05$.

RESULTS

General characteristics

A total of 100 patients with COPD participated in the study. The mean age was 67.3 ± 6.8 years. The patients were predominantly male (54%), literate (68%), and Catholic (77%). Comorbidity was present in 36% of the sample (Table 1). The mean positive RC score and the mean negative RC score were 27.17 ± 1.60 and 8.21 ± 2.12, respectively. Positive RC scores were found to be significantly higher than were negative RC scores (p = 0.01), demonstrating that the patients with COPD more often employed positive RC strategies to deal with their disease. The sociodemographic and clinical characteristics of the sample are described in Table 1.

When assessing RC among patients with COPD by gender, level of education, religion, and presence of comorbidities, we found a significant difference only for gender, showing that women employed positive RC more often than did men (27.5 ± 1.1 vs. 26.8 ± 2.8; p = 0.02).

Religious coping in patients with COPD and healthy individuals

No statistically significant difference was found in positive RC between patients with COPD and healthy individuals, with medians [IQR] of 28 [27-28] and 28 [28-28], respectively (p = 0.08). However, negative RC scores were significantly higher in patients with COPD than in healthy individuals: 8 [7-8] and 7 [7-7], respectively (p = 0.01).

Factors associated with religious coping in patients with COPD

Negative RC showed an inverse association with 6MWD (r = −0.3; p < 0.05) and a direct association with depressive symptoms (r = 0.2; p < 0.03; Table 2). No significant correlations were observed between negative RC and any of the other variables studied. Positive RC correlated significantly with none of the variables studied.

Multiple linear regression analysis was performed to identify independent variables strongly associated with negative RC (dependent variable). The independent variables selected were statistically significant in the univariate analysis. The model was built taking into account confounding variables and collinearity. The variables that explained the variance in negative RC in a linear fashion were identified by using a backward stepwise process (Table 3). The 6MWD was most strongly associated with negative RC (coefficient = −0.009; 95% CI: −0.01 to −0.003), which explained 35% of the variance in negative RC.

Table 1. Sociodemographic characteristics and clinical variables of the sample of patients with COPD.[a]

Variable	(N = 100)
Age, years	67.3 ± 6.8
Gender	
Male	54 (54)
Female	46 (46)
Marital status	
Single	7 (7)
Married	67 (67)
Separated	9 (9)
Widowed	17 (17)
Level of education	
Literate	68 (68)
Illiterate	32 (32)
Religion	
Catholic	77 (77)
Non-Catholic	23 (23)
BMI, kg/cm^2	25 ± 4.8
Comorbidities	
Yes	36 (36)
No	64 (64)
Spirometry	
Post-BD FEV_1, % of predicted	45.4 ± 12.6
Post-BD FVC, % of predicted	61.3 ± 15.1
6MWD, m	368.5 ± 76.1
Religious coping	
Positive	28 [27-28]
Negative	7 [7-8]
CAT	18.6 ± 8.2
SGRQ	
Symptoms	45.4 ± 21.1
Activity	64.4 ± 20.9
Psychosocial impact	43.7 ± 19.8
Total	51.7 ± 16.01
SF-36	
PCS	39.25 ± 15.28
MCS	51.28 ± 11.83
PHQ-9	9 ± 5.8

BMI: body mass index; BD: bronchodilator; 6MWD: six-minute walk distance; CAT: COPD Assessment Test; SGRQ: Saint George's Respiratory Questionnaire; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; PCS: physical component summary; MCS: mental component summary; and PHQ-9: Patient Health Questionnaire-9. [a]Values expressed as n (%), mean ± SD, or median [interquartile range].

DISCUSSION

The present study showed that patients with COPD more significantly employ positive RC to deal with their disease. The use of a positive strategy reflects a secure relationship with a transcendental force and a benevolent view of the world. Negative RC (spiritual conflict) was less common in the sample. However, when used, it was found to be associated with disease severity as measured by 6MWD and with psychological distress.

When comparing RC in patients with COPD and healthy individuals, we found that both groups had similar positive RC scores. However, we found that negative RC scores were significantly higher in the COPD group. This reflects the spiritual suffering of the patients who, in the face of illness, feel dissatisfaction

Table 2. Correlation between religious coping and demographic and clinical data in patients with COPD.

Variable	Positive RC		Negative RC	
	r	p	r	p
Age	−0.02	0.8	−0.12	0.2
Post-BD FEV_1 (% of predicted)	0.03	0.7	−0.05	0.6
6MWD	0.18	0.06	−0.34	< 0.04
SGRQ				
Symptoms	−0.06	0.5	0.11	0.2
Activity	0.03	0.7	0.10	0.2
Psychosocial impact	−0.08	0.4	−0.05	0.5
Total	−0.06	0.5	0.04	0.6
CAT	−0.03	0.7	−0.04	0.6
SF-36				
PCS	−0.03	0.7	−0.14	0.1
MCS	0.06	0.5	−0.10	0.2
PHQ-9	0.03	0.6	0.21	0.03

RC: religious coping; BD: bronchodilator; 6MWD: six-minute walk distance; SGRQ: Saint George's Respiratory Questionnaire; CAT: COPD Assessment Test; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; PCS: physical component summary; MCS: mental component summary; and PHQ-9: Patient Health Questionnaire-9.

Table 3. Multivariate linear regression analysis of negative religious coping and clinical variables of the sample.

Outcome/Variable	Coefficient	Standard error	t	p	95% CI
Negative religious coping					
Constant	11.07	1.23	8.94	< 0.01	8.61-13.52
6MWD	−0.009	0.003	−3.01	0.003	−0.01 to −0.003

6MWD: six-minute walk distance.

with God, which leads them to redefine the stressor as a divine punishment.[21]

In the present study, women were found to employ positive RC more often than men. Culturally, women are more resilient and, therefore, use positive RC strategies to deal with stress.[22] In a recent systematic review, Veit et al.[23] reported greater use of positive RC in women with breast cancer.

The results of the present study demonstrate that there is a statistically significant correlation between negative RC and depressive symptoms in patients with COPD, which corroborates the findings of previous studies involving patients with emphysema[9] and patients with chronic lung disease being evaluated for lung transplantation.[11] In the latter study,[11] the authors pointed out that, although the patients were severely ill, no significant levels of depression were found, which was explained by the prospect of cure after the transplantation process. Yohannes et al.[24] stated that the mechanism determining the common association of COPD with depression has not yet been properly identified.

In the present study, negative RC scores showed an inverse and statistically significant correlation with exercise capacity as measured by 6MWD, which is an important predictor of disease severity.[25] This demonstrates that the impairment caused by COPD seems to have an important relationship with the coping strategy used by the patient. Burker et al.[26] reported frequent use of negative RC strategies in the face of important outcomes in patients with chronic lung disease being evaluated for lung transplantation.

No significant correlations were found between RC and pulmonary function or QoL, which is in contrast to the findings of previous studies.[9,27] Pedersen et al.[27] stated that negative RC was associated with poor QoL in patients with COPD. Perhaps one reason why our study did not demonstrate such an association was that our patients rarely employed negative RC.

The results of the present investigation show health care professionals the importance of assessing religiosity in patients with COPD who are treated in health care facilities, especially to identify those who employ negative RC, because this is related to psychological distress and disease severity. Following this line of reasoning, research addressing RC in a focused and specific manner should include the search for spiritual and religious support.[27]

Some strengths of the present study include the assessment of RC strategies in patients with COPD, a topic that has been addressed by few studies, and the determination of whether these strategies are associated with clinical variables. In addition, the study supports that RC can be one more strategy in approaching these patients and adds to the current literature by providing one more source of information for future studies using a similar approach. Among the limitations of the study is its cross-sectional design, which precludes further causal inferences. Since this was a convenience sample, generalization is unwarranted.

In addition, the lack of a qualitative approach can also be considered a limitation, given that combining such an approach with the quantitative method would allow a more detailed understanding of patient perceptions of how religiosity is experienced and dealt with in the context of their health status.

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ORIGINAL ARTICLE

The Brazilian Portuguese-language version of the Manchester Respiratory Activities of Daily Living questionnaire: construct validity, reliability, and measurement error

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ABSTRACT

Objective: To test the construct validity, reliability, and measurement error of the Brazilian Portuguese-language version of the Manchester Respiratory Activities of Daily Living (MRADL) questionnaire in patients with COPD. **Methods:** We evaluated 50 patients with COPD, among whom 30 were men, the mean age was 64 ± 8 years, and the median FEV_1 as a percentage of the predicted value (FEV_1%predicted) was 38.4% (interquartile range, 29.1-57.4%). Pulmonary function and limitations in activities of daily living (ADLs) were assessed by spirometry and by face-to-face application of the MRADL, respectively. For the construct validity analysis, we tested the hypothesis that the total MRADL score would show moderate correlations with spirometric parameters. We analyzed inter-rater reliability, test-retest reliability, inter-rater measurement error, and test-retest measurement error. **Results:** The total MRADL score showed moderate correlations with the FEV_1/FVC ratio, FEV_1 in liters, FEV1%predicted, and FVC%predicted, all of the correlations being statistically significant ($r = 0.34$, $r = 0.31$, $r = 0.42$, and $r = 0.38$, respectively; $p < 0.05$ for all). For the reliability and measurement error of the total MRADL score, we obtained the following inter-rater and test-retest values, respectively: two-way mixed-effects model intraclass correlation coefficient for single measures, 0.92 (95% CI: 0.87-0.96) and 0.89 (95% CI: 0.81-0.93); agreement standard error of measurement, 1.03 and 0.97; smallest detectable change at the individual level, 2.86 and 2.69; smallest detectable change at the group level, 0.40 and 0.38; and limits of agreement, −2.24 to 1.96 and −2.65 to 2.69. **Conclusions:** In patients with COPD in Brazil, this version of the MRADL shows satisfactory construct validity, satisfactory inter-rater/test-retest reliability, and indeterminate inter-rater/test-retest measurement error.

Keywords: Pulmonary disease, chronic obstructive; Activities of daily living; Disability evaluation; Patient reported outcome measures; Validation studies.

INTRODUCTION

Patient-reported outcomes are status reports of the health of a patient that come directly from the patient, without interpretation of the patient response by a clinician or anyone else.[1] They facilitate communication between patients and health care providers, as well as allowing the assessment of the impact that diseases or treatments have on the lives of patients.[2] Patient-reported outcome measures (PROMs) are recognized assessment tools in patients with COPD. The evaluation of physical functioning by PROMs enables us to understand the impact of COPD on activities of daily living (ADLs) from the patient perspective.[3] With the progression of the disease, patients experience limitations in activities they choose to engage in on a day-to-day basis,[4] which may lead to social isolation and increased dependency on caregivers.[5] Therefore, measuring limitations in ADLs is important to the monitoring of disease progression, the planning of appropriate interventions, and the evaluation of treatment responses.[6]

The Manchester Respiratory Activities of Daily Living questionnaire (MRADL) is one of the physical disability PROMs for assessing ADL limitations in patients with COPD.[6-9] The MRADL is a disease-specific assessment tool that is valid, reliable, and responsive to pulmonary rehabilitation,[10] as well as being a predictor of premature death in patients with COPD.[11,12] Although the MRADL has been translated into Portuguese and cross-culturally

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adapted for use in the COPD population of Brazil,[13] it has yet to be validated in that population. The objective of this study was to determine the construct validity, reliability, and measurement error of the Brazilian Portuguese-language version of the MRADL in patients with COPD. We hypothesized that the total MRADL score would (in the construct validity analysis) show moderate positive correlations with five spirometric parameters: the FEV_1/FVC ratio, FEV_1 in liters, FEV_1 as a percentage of the predicted value (FEV_1%predicted), FVC in liters, and FVC%predicted.

METHODS

Patient selection

Patients with a confirmed diagnosis of COPD who were referred to a public outpatient clinic specializing in COPD were considered eligible for inclusion in the study. The inclusion criteria were as follows: moderate (grade 2), severe (grade 3), or very severe (grade 4) airflow limitation and optimized medication in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[14]; being ≥ 40 years of age; and being a current or former smoker. Patients who had ADL limitations caused by other respiratory diseases, cardiovascular diseases, neurological disorders, musculoskeletal disorders, rheumatic diseases, or other conditions were excluded, as were those who were currently participating in a pulmonary rehabilitation program or had participated in one in the last 6 months prior to the study, those with a Mini-Mental State Examination score indicative of impaired cognition (< 24 or < 19 for literate and illiterate subjects, respectively),[15] and those who reported a COPD exacerbation or a change in ADL limitations in the month prior to the study or during data collection. The study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (CAAE no. 33299214.8.0000.0121). All participating patients gave written informed consent.

Study design

We carried out pulmonary function testing in accordance with the American Thoracic Society and European Respiratory Society spirometry standards,[16] using a portable spirometer (EasyOne; ndd Medical Technologies, Inc., Zurich, Switzerland). We obtained postbronchodilator measures of the FEV_1/FVC ratio, FEV_1 in liters, and FVC in liters, using the equations devised by Pereira et al.[17] to determine the percentages of the predicted values. The severity of airflow limitation was classified, in accordance with the FEV_1%predicted, as GOLD grade 2 (50% ≤ FEV_1 < 80%), GOLD grade 3 (30% ≤ FEV_1 < 50%), or GOLD grade 4 (FEV_1 < 30%), assuming an FEV_1/FVC ratio < 0.7.[14]

The MRADL was used in order to assess ADL limitations. It consists of 21 items, in four domains—mobility (7 items), kitchen activities (4 items), domestic tasks (6 items), and leisure activities (4 items). The total MRADL score ranges from 0 to 21, and a maximum score indicates no physical impairment.[10,13] Two raters (designated raters 1 and 2) each read the MRADL instructions and items to the patients with an interval of approximately 10 min between the two administrations. Rater 1 administered the MRADL to the same patients again after an interval of 1-2 weeks.[18] All three administrations were carried out independently in an outpatient setting.

Statistical analysis

Data normality was analyzed by the Shapiro-Wilk test. For correlation analysis between MRADL scores and spirometric variables, Spearman's correlation coefficient (r) was used. On the basis of evidence in the literature, we expected the total MRADL score to show moderate[19] positive correlations with the FEV_1/FVC ratio, FEV_1 in liters, FEV_1%predicted, FVC in liters, and FVC%predicted. To compare the MRADL scores between the raters and between the test and retest, the Wilcoxon test was used. Inter-rater and test-retest reliability of the MRADL scores were analyzed by calculating the two-way mixed-effects model intraclass correlation coefficient for single measures—ICC(3,1)—and the corresponding 95% confidence interval. For analysis of the inter-rater and test-retest measurement errors, we calculated the agreement standard error of measurement ($SEM_{agreement}$); the smallest detectable change at the individual and group levels ($SDC_{individual}$ and SDC_{group}, respectively); and the limits of agreement (LoA). To visualize the total score and agreement between the MRADL measurements, Bland-Altman plots were used.[20] Values of $p < 0.05$ were considered statistically significant.

RESULTS

We evaluated 50 patients with COPD, 30 of whom were men. All eligible patients were included in the study (i.e., none were excluded). The severity of airflow limitation was stratified by the GOLD criteria: grade 2, in 15 patients (30.0%); grade 3, in 22 (44.0%); and grade 4, in 13 (26.0%).[14] The general characteristics of the sample are presented in Table 1.

All of the patients completed all of the items on the MRADL. As shown in Figure 1, the total MRADL score correlated moderately with four of the five spirometric variables evaluated. Some of the MRADL domain scores also showed moderate correlations with spirometric variables: the kitchen activities domain score correlated with the FEV_1/FVC ratio ($r = 0.45$; $p < 0.01$), FEV_1 in liters ($r = 0.38$; $p < 0.05$), FEV_1%predicted ($r = 0.43$; $p < 0.01$), and FVC%predicted ($r = 0.29$; $p < 0.05$); the domestic tasks domain score correlated with the FEV_1/FVC ratio ($r = 0.41$; $p < 0.01$), FEV_1 in

Table 1. General characteristics of the sample.

Characteristic	(N = 50)
Age (years), mean ± SD (95% CI)	64 ± 8 (62-66)
BMI (kg/m^2), mean ± SD (95% CI)	24.6 ± 5.0 (23.2-26.1)
Smoking history (pack-years), median (IQR)	48 (32-80)
FEV_1/FVC ratio, median (IQR)	0.46 (0.38-0.56)
FEV_1 (L), median (IQR)	1.07 (0.79-1.43)
FEV_1 (% predicted), median (IQR)	38.4 (29.1-57.4)
FVC (L), median (IQR)	2.26 (1.96-2.90)
FVC (% predicted), median (IQR)	64.8 (56.3-72.9)

BMI: body mass index; and IQR: interquartile range.

liters ($r = 0.30$; $p < 0.05$), FEV_1%predicted ($r = 0.45$; $p < 0.01$), and FVC%predicted ($r = 0.38$; $p < 0.05$); and the leisure activities domain score correlated with FEV_1 in liters ($r = 0.30$; $p < 0.05$), FEV_1%predicted ($r = 0.31$; $p < 0.05$), and FVC%predicted ($r = 0.29$; $p < 0.05$). All of the MRADL scores are shown in Table 2, as are the inter-rater and test-retest values for ICC(3,1), $SEM_{agreement}$, $SDC_{individual}$, and SDC_{group}. As can be seen in Table 2, no inter-rater or test-retest differences were observed for the MRADL scores ($p > 0.05$ for all). The inter-rater and test-retest LoA for the total MRADL score are plotted in Figure 2. The respective inter-rater and test-retest LoA values for the MRADL domain scores were as follows: for the mobility domain score, −1.19 to 1.03 and −1.32 to 1.36; for the kitchen activities domain score, −1.00 to 1.08 and −1.24 to 1.20; for the domestic tasks domain score, −0.92 to 0.84 and −0.91 to 1.19; and for the leisure activities domain score, −1.21 to 1.09 and −1.41 to 1.17.

DISCUSSION

In this study, we assessed the Brazilian Portuguese-language version of the MRADL, evaluating its construct validity, reliability, and measurement error using repeated measurements. To our knowledge, this is the first study to describe the measurement properties of this version of the MRADL.

As expected, moderate correlations were observed between the total MRADL score and spirometric variables, four of our five hypotheses being accepted. Therefore, we rated the construct validity of the instrument for use in patients with COPD in Brazil as satisfactory according to the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN),[21] considering the relationship its total score showed with the FEV_1/FVC ratio, FEV_1 in liters, FEV_1%predicted, and FVC%predicted. In addition, the MRADL scores for the kitchen activities, domestic tasks, and leisure activities domains also correlated with most of the spirometric variables. In other validation studies, similar correlations have been observed between the ADL limitation and lung function constructs: the total COPD Activity Rating Scale score has been shown to correlate positively with the FEV_1 in liters, FEV_1%predicted, and FVC in liters[22]; the total London Chest Activity of Daily Living scale score has been shown to correlate negatively with the FVC in liters[23]; and the total Functional Performance Inventory score has been shown to correlate positively with the FEV_1%predicted.[24]

The study evaluating the measurement properties of the original MRADL demonstrated that its total score is accurate in discriminating patients with an FEV_1%predicted < 60% from healthy controls (without lung diseases or respiratory symptoms).[10] The authors of that study found that the FEV_1/FVC ratio was one of the predictors of the total MRADL score, explaining 2% of its variance.[10] Determining the FEV_1/FVC ratio is fundamental to establishing a diagnosis of COPD, whereas determining the FEV_1 is a necessary part of assessing the severity of airflow limitation.[14] Lung function should be considered a primary endpoint in clinical research on the efficacy of medications for the treatment of COPD.[25] In the absence of other widely accepted, validated clinical markers, spirometric variables have been used as global markers of pathophysiological changes in COPD,[26] underscoring the relevance of the relationship between lung function and ADL limitation.

In the present study, we determined the ICC(3,1), $SEM_{agreement}$, $SDC_{individual}$, SDC_{group}, and LoA values for the use of the MRADL in patients with COPD in Brazil. The inter-rater and test-retest reliabilities of the MRADL (total and domain scores) were rated against the COSMIN criteria[21] and were found to be satisfactory, because the ICC(3,1) values were higher than 0.7 for all of the domain scores, except the test-retest ICC(3,1) for the kitchen activities domain score, which was exactly 0.70. However, the inter-rater and test-retest measurement errors of the MRADL scores would be rated as indeterminate in accordance with the COSMIN guideline for systematic reviews of PROMs,[21] given that the minimal important change value does not yet exist for the classification of SDC and LoA values. In another study, the observed inter-rater and test-retest ICC values (0.92 for both) were shown to be similar to the test-retest value for the total score on the MRADL administered by post, whereas the

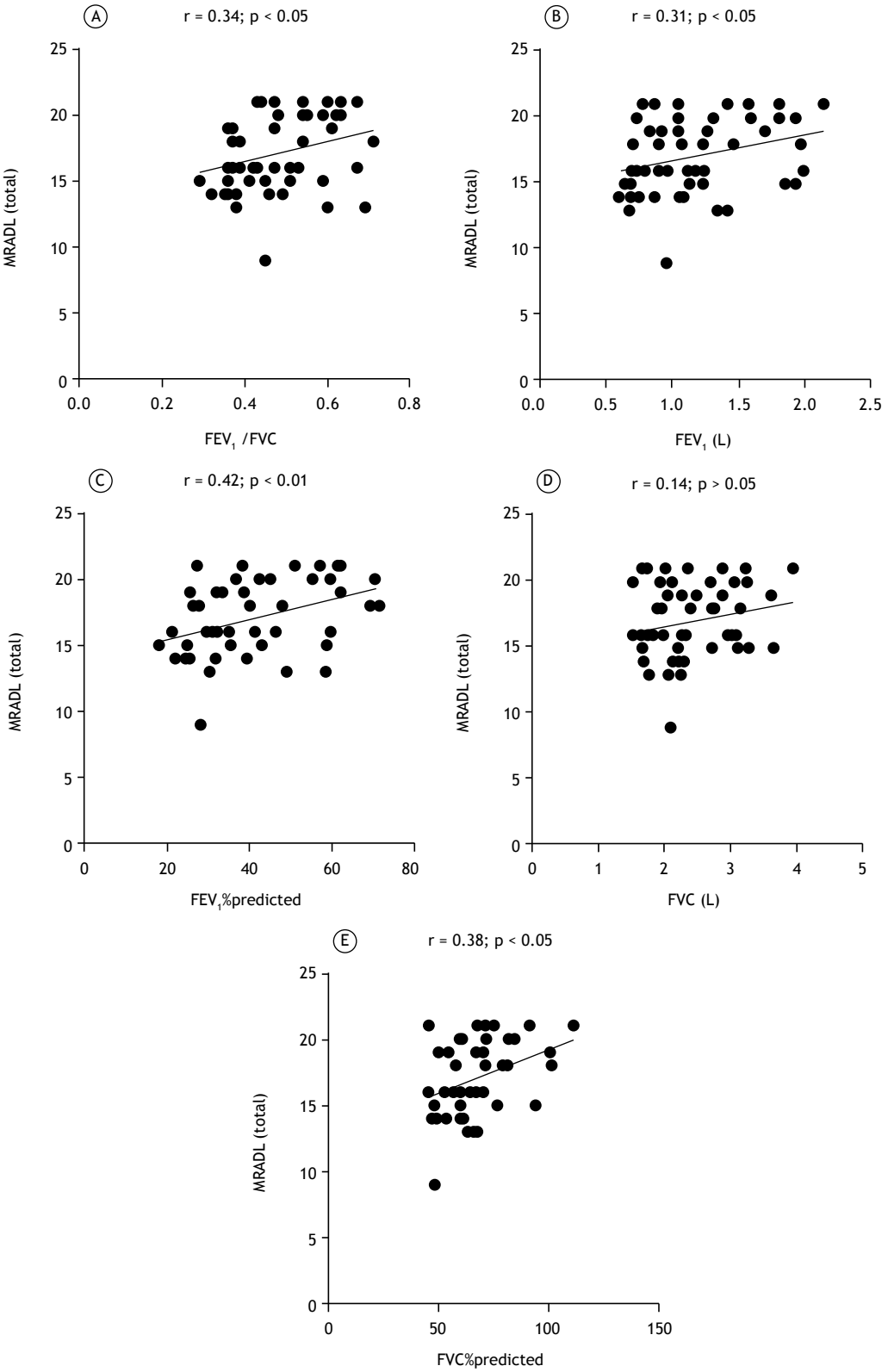

Figure 1. Correlations of the total score on the Manchester Respiratory Activities of Daily Living questionnaire (MRADL) with the FEV_1/FVC ratio (in A); FEV_1 in liters (in B); FEV_1 as a percentage of the predicted value (FEV_1%predicted, in C); FVC in liters (in D); and FVC%predicted (in E).

Table 2. Scores, reliability, and measurement error of the Brazilian Portuguese-language version of the Manchester Respiratory Activities of Daily Living questionnaire.

MRADL domain	Score		ICC(3,1)	$SEM_{agreement}$	SDC		Score	ICC(3,1)	$SEM_{agreement}$	SDC	
	Rater 1[a]	Rater 2					Rater 1[b]				
	Median (IQR)	Median (IQR)*	Value (95% CI)		Individual	Group	Median (IQR)*	Value (95% CI)		Individual	Group
Total	16 (15-20)	17 (15-20)	0.92 (0.87-0.96)	1.03	2.86	0.40	17 (15-20)	0.89 (0.81-0.93)	0.97	2.69	0.38
Mobility	7 (6-7)	7 (6-7)	0.80 (0.67-0.88)	0.57	1.57	0.22	7 (6-7)	0.75 (0.59-0.85)	0.49	1.37	0.19
Kitchen activities	4 (3-4)	4 (3-4)	0.76 (0.61-0.86)	0.43	1.18	0.17	4 (3-4)	0.70 (0.53-0.82)	0.45	1.25	0.18
Domestic tasks	4 (3-6)	5 (3-5)	0.95 (0.91-0.97)	0.38	1.04	0.15	4 (3-6)	0.93 (0.88-0.96)	0.80	2.21	0.31
Leisure activities	3 (2-4)	3 (2-4)	0.80 (0.67-0.88)	0.51	1.42	0.20	3 (3-4)	0.73 (0.57-0.84)	0.76	2.11	0.30

MRADL: Manchester Respiratory Activities of Daily Living questionnaire; ICC(3,1): two-way mixed-effects model intraclass correlation coefficient for single measures; $SEM_{agreement}$: agreement standard error of measurement; and SDC: smallest detectable change. Test. [b]Retest. *$p > 0.05$ vs. rater 1 (test, not retest) for all domain scores and for the total score.

SEM and LoA values were shown to be lower (1.55) and higher (−0.69 to 0.54), respectively.[27] However, the authors of that study used different parameters of reliability and measurement error (the one-way random effects model ICC and consistency SEM).[27]

In a previous systematic review,[6] the lack of detailed information about the measurement properties of tools designed to assess ADL limitations in patients with COPD was one of the main problems identified. A few studies have been conducted to determine the measurement properties of disease-specific PROMs for ADL limitations in patients with COPD in Brazil.[28,29]

Our study has some limitations. First, the construct validity analysis was limited to the hypothesis of a relationship between ADL limitations and lung function. Our results support that hypothesis, except for the fact that we identified no significant correlation between the total MRADL score and FVC in liters. It is known that the FVC may not be discriminative; in patients with obstructive lung disease, it is usually reduced to a lesser degree or even normal. It is also known that the FVC value in liters may be nonspecific, because it is not corrected for age, height, gender, or ethnicity (i.e., by a reference equation). In addition, the absence of a correlation between the total MRADL score and FVC in liters could also be due to a type II error, despite the fact that our sample size was within the limits of what is considered satisfactory.[30] Additional studies could test other hypotheses related to the construct validity of the instrument. Furthermore, the adequacy of the MRADL measurement error can only be attested to when studies on interpretability provide its minimal important change value. Nevertheless, the present study is unprecedented in that it details the measurement properties of the Brazilian Portuguese-language version of the MRADL.

In conclusion, the Brazilian Portuguese-language version of the MRADL has sufficient construct validity for use in patients with COPD in Brazil, given that our findings support our hypotheses about the specific relationship between ADL limitations and lung function. In addition, this version of the MRADL is sufficiently reliable; that is, it is able to distinguish ADL limitation between patients with COPD, even when applied by different raters on the same occasion and when applied twice within a short period of time. Furthermore, the present study provides inter-rater and test-retest measurement error parameters, which refer to the systematic and random error of the scores of patients with COPD that is not attributed to true changes in ADL limitations, for this version of the MRADL. To date, the measurement error of the MRADL for Brazilians with COPD is considered indeterminate. Further studies should be conducted to evaluate other measurement properties of the instrument in this population.

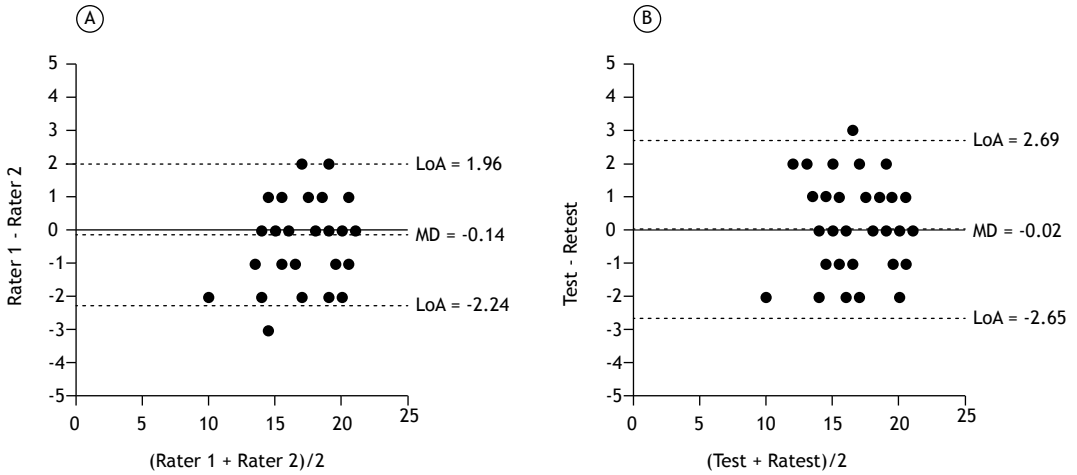

Figure 2. Bland Altman plots of the total score on the Manchester Respiratory Activities of Daily Living questionnaire, showing the inter-rater reliability (A) and test-retest reliability (B). LoA: limit of agreement; and MD: mean difference.

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Clinical and functional correlations of the difference between slow vital capacity and FVC

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ABSTRACT

Objective: To evaluate the relationship that the difference between slow vital capacity (SVC) and FVC (ΔSVC-FVC) has with demographic, clinical, and pulmonary function data. **Methods:** This was an analytical cross-sectional study in which participants completed a respiratory health questionnaire, as well as undergoing spirometry and plethysmography. The sample was divided into two groups: ΔSVC-FVC ≥ 200 mL and ΔSVC-FVC < 200 mL. The intergroup correlations were analyzed, and binomial logistic regression analysis was performed. **Results:** The sample comprised 187 individuals. In the sample as a whole, the mean ΔSVC-FVC was 0.17 ± 0.14 L, and 61 individuals (32.62%) had a ΔSVC-FVC ≥ 200 mL. The use of an SVC maneuver reduced the prevalence of nonspecific lung disease and of normal spirometry results by revealing obstructive lung disease (OLD). In the final logistic regression model (adjusted for weight and body mass index > 30 kg/m^2), OLD and findings of air trapping (high functional residual capacity and a low inspiratory capacity/TLC ratio) were predictors of a ΔSVC-FVC ≥ 200 mL. The chance of a bronchodilator response was found to be greater in the ΔSVC-FVC ≥ 200 mL group: for FEV1 (OR = 4.38; 95% CI: 1.45-13.26); and for FVC (OR = 3.83; 95% CI: 1.26-11.71). **Conclusions:** The use of an SVC maneuver appears to decrease the prevalence of nonspecific lung disease and of normal spirometry results. Individuals with a ΔSVC-FVC ≥ 200 mL, which is probably the result of OLD and air trapping, are apparently more likely to respond to bronchodilator administration.

Keywords: Vital capacity; Plethysmography; Airway obstruction.

INTRODUCTION

American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines recommend the use of slow VC (SVC) as the denominator to calculate the Tiffeneau index.[1] Despite this recommendation, SVC maneuvers are not routinely used in most pulmonary function laboratories in Brazil.

VC is determined by measuring the volume of air in the lungs after a maximal inhalation and after a maximal exhalation, i.e., TLC and RV, respectively, which include lung/chest wall compliance and elastic recoil, respiratory muscle strength, alveolar collapse, and airway closure.[2-4] In individuals with no chest wall or respiratory muscle abnormalities, TLC is determined by lung elastic recoil.[5] In young individuals, RV is primarily determined by static factors (chest wall elastic recoil and respiratory muscle pressure), whereas, in elderly individuals and in those presenting with airflow limitation, RV is determined by dynamic factors (expiratory flow limitation and airway closure).[3,6]

In normal individuals, VC reflects the properties of the lung parenchyma, whereas, in those with chronic obstructive lung disease, it reflects the properties of the airways.[5] In patients with airflow limitation, airway closure occurs at high lung volumes.[7] During an FVC maneuver, dynamic compression and airway collapse can lead to premature airway closure, thus reducing FVC. Reduced thoracic gas compression during an SVC maneuver explains the fact that, even in healthy individuals, there is a difference between SVC and FVC (ΔSVC-FVC), which is more pronounced in patients with obstructive lung disease (OLD).[5]

Few studies have examined the association of ΔSVC-FVC with demographic characteristics, lung function, respiratory symptoms, and lung disease.[4,8-10] To our knowledge, there have been no studies evaluating bronchodilator response in relation to ΔSVC-FVC.

The primary objective of the present study was to examine the association of ΔSVC-FVC with demographic variables, spirometric parameters, plethysmographic parameters, bronchodilator response, and lung function, as well as to identify factors independently associated with a ΔSVC-FVC ≥ 200 mL. A secondary objective was to examine the association of ΔSVC-FVC with the severity of OLD, respiratory symptoms, and clinical diagnosis, as well as to compare the spirometry results obtained with the use of FVC maneuvers alone and those obtained with the combined use of FVC and SVC maneuvers.

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METHODS

This was an analytical cross-sectional study. The study sample consisted of patients referred for pulmonary function testing between October 21, 2013 and July 28, 2015 at the *Instituto de Assistência Médica ao Servidor Público Estadual* (IAMSPE, Institute for the Medical Care of State Civil Servants), located in the city of São Paulo, Brazil. The study was approved by the Research Ethics Committee of the IAMSPE (Ruling no. 373,763, August 5, 2013).

Patients were randomly invited to participate in the study, and those who agreed gave written informed consent and completed a respiratory questionnaire,[11] which was administered by a nurse who is also a pulmonary function technician certified by the Brazilian Thoracic Association.

The inclusion criteria were being an outpatient and meeting the criteria established in studies reporting reference values for spirometry and plethysmography in Brazil.[12,13] The exclusion criteria were having performed spirometric or plethysmographic maneuvers that failed to meet the ATS/ERS acceptability and reproducibility criteria[14,15] and presenting with SVC < FVC.

Figure 1 shows a flow chart of the sample selection process. All participants performed SVC, FVC, and plethysmographic maneuvers (in this order) using a Collins system (Ferraris Respiratory, Louisville, CO, USA). All tests were performed by the aforementioned nurse, with participants in a sitting position and wearing a nose clip.

All tests were reviewed by the principal investigator and the coordinator of the pulmonary function laboratory. Emphasis was placed on the quality of inspiratory capacity (IC) maneuvers, which were performed in a relaxed manner after at least three stable breaths. IC was defined as the average of three reproducible measurements (a variability of ≤ 100 mL). The highest SVC value was selected from three measurements with a reproducibility of ≤ 100 mL. During FVC maneuvers, the difference between the two highest FVC and FEV_1 values was ≤ 150 mL and that between the two highest PEF values was ≤ 10%. The highest FVC and FEV_1 values were selected from those obtained during acceptable maneuvers, in accordance with the criterion of PEF reproducibility.[14,16]

With regard to plethysmography, functional residual capacity (FRC) was calculated from thoracic gas volume, at the end of tidal volume exhalation. TLC and RV were calculated by the following formulas: TLC = IC + FRC and RV = TLC − SVC.[15]

The results were interpreted in accordance with the ATS/ERS criteria.[1] Spirometry results were considered normal when values were above the lower limit of normal; OLD was defined as an FEV_1/(F)VC ratio below the lower limit of normal; nonspecific lung disease (NLD) was defined as a proportional reduction in (F)VC and FEV_1; and OLD with reduced (F)VC was defined as the presence of OLD associated with a reduction in (F)VC. First, we analyzed the spirometry results obtained with the use of FVC maneuvers alone; then, we analyzed those obtained with the combined use of FVC and SVC maneuvers.

Plethysmographic variables were then analyzed. Given that specific airway conductance (sGaw) is also a parameter of airflow limitation, sGaw values of < 0.12 [with or without reduced FEV_1/(F)VC ratio] were interpreted as indicative of OLD.[17,18] Air trapping was defined as an RV > 130%, and lung hyperinflation was defined as a TLC > 120%. All patients with reduced TLC were diagnosed with restrictive lung disease.[19] In such cases, the use of a fixed threshold is acceptable because of decreasing dispersion of the data around the predicted equation line.[20] The difference between TLC and FVC, a theoretical measure designated forced RV (FRV), was calculated and expressed as absolute values and as a percentage of the predicted values.

OLD was classified as mild (FEV_1 ≥ 60%), moderate (FEV_1 = 41-59%), or severe (FEV_1 ≤ 40%), in accordance with British Thoracic Society criteria.[21]

A subgroup of patients with OLD underwent spirometry 20 min after administration of a bronchodilator (400 µg of albuterol aerosol). A significant bronchodilator response was characterized by FVC and FEV_1 ≥ 200 mL and ≥ 7% of predicted; SVC ≥ 250 mL and ≥ 8% of predicted; and IC ≥ 300 mL.[22]

The study sample was divided into two groups: ΔSVC-FVC < 200, comprising patients in whom ΔSVC-FVC was < 200 mL (as assessed before bronchodilator administration); and ΔSVC-FVC ≥ 200, comprising patients in whom ΔSVC-FVC was ≥ 200 mL (as assessed before bronchodilator administration). The 200-mL threshold was used because it is higher than that used in order to assess reproducibility, as well as being higher than the mean ΔSVC-FVC values observed in healthy individuals.[8,9,23]

Statistical analysis

All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Data were expressed as means and standard deviations for quantitative variables and as absolute numbers and proportions for categorical variables. Normality of data distribution was assessed with the Kolmogorov-Smirnov test with Lilliefors correction.

Functional, demographic, and clinical parameters were compared between the groups with the use of the Student's t-test (for data with normal distribution) or the Mann-Whitney U test (for data with non-normal distribution). The kappa statistic was used in order to assess the agreement between the spirometry results obtained with FVC maneuvers alone and those obtained with FVC and SVC maneuvers in combination. Categorical variables were compared by the chi-square test or Fisher's exact test.

Correlations of ΔSVC-FVC with demographic, clinical, and functional variables were analyzed with Pearson's or Spearman's correlation coefficient, the former being

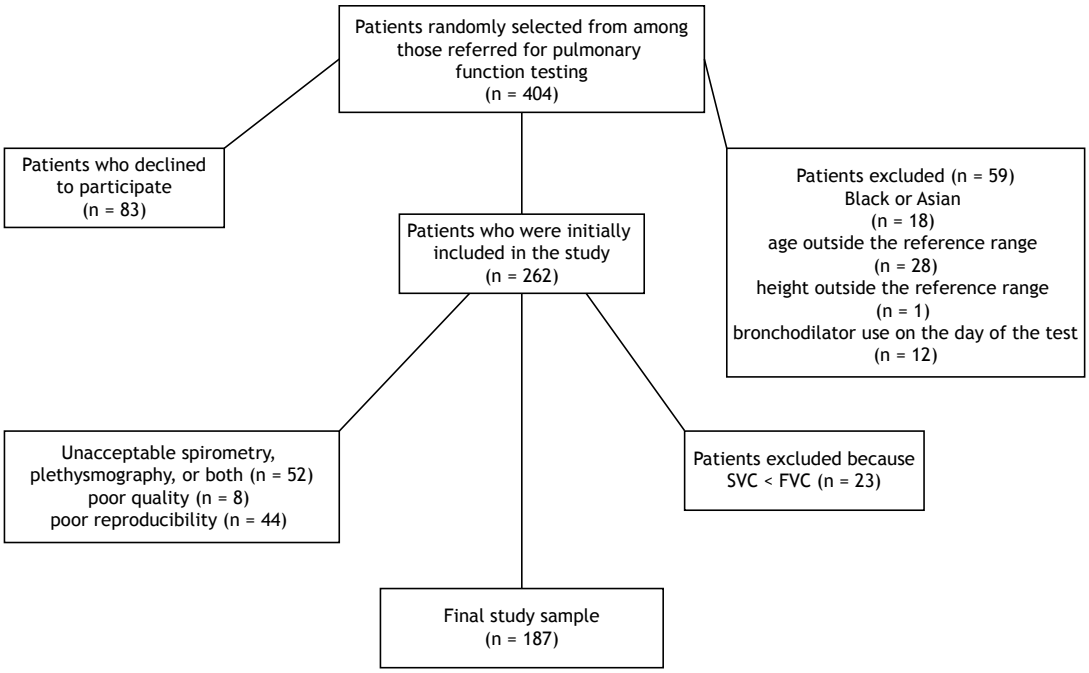

Figure 1. Flow chart of the sample selection process. SVC: slow vital capacity.

used for data with normal distribution and the latter being used for data with non-normal distribution.

Logistic regression analysis was performed to identify independent predictors of a ΔSVC-FVC ≥ 200 mL. First, a single logistic regression analysis was performed to determine the OR for each demographic variable. Then, a binomial logistic regression analysis was performed to evaluate spirometric and plethysmographic parameters, crude and adjusted ORs being calculated (for the variables that were significant in the single logistic regression model) to predict a ΔSVC-FVC ≥ 200 mL.

A multiple logistic regression analysis was performed to determine whether a ΔSVC-FVC ≥ 200 mL was a predictor of significant changes in spirometric parameters (FEV_1, FVC, SVC, and IC) after bronchodilator administration. It was also used in order to determine whether a ΔSVC-FVC ≥ 200 mL was predictive of normal TLC in cases in which spirometry results were indicative of NLD or of OLD with reduced FVC and a significant bronchodilator response. The level of significance was set at 5% for all analyses except the single logistic regression model, in which the level of significance was set at $p < 0.20$.

RESULTS

A total of 187 patients were selected (Figure 1). The general characteristics of the recruited population and a comparison between the two study groups are shown in Table 1. The mean age was 59.01 ± 12.80 years, and 126 patients (67.40%) were female. Mean height and weight were 159.90 ± 9.60 cm and 78.46 ± 18.48 kg, respectively. Mean ΔSVC-FVC was 0.17 L, a ΔSVC-FVC ≥ 200 mL being observed in 61 participants (32.62%). A ΔSVC-FVC ≥ 200 mL was observed in 28 (45.90%) of the 61 male participants and in 33 (26.20%) of the 126 female participants ($p = 0.007$). Height and weight were higher in the ΔSVC-FVC ≥ 200 group than in the ΔSVC-FVC group < 200 ($p = 0.002$ and $p = 0.017$, respectively). There were no significant differences between the two groups regarding body mass index (BMI) or clinical parameters (smoking and dyspnea). The Tiffeneau index was lower in the ΔSVC-FVC ≥ 200 group than in the ΔSVC-FVC < 200 group, whereas lung volumes were higher in the former than in the latter. A ΔSVC-FVC was significantly more common in patients with OLD, regardless of the severity of airflow obstruction.

Table 2 shows the agreement between the spirometry results obtained with FVC maneuvers alone and those obtained with FVC and SVC maneuvers in combination (kappa = 0.653). Of the 73 normal spirometry results obtained when FVC maneuvers were used in isolation, 21 were reclassified as OLD when FVC and SVC maneuvers were used in combination. Of the 32 cases that were diagnosed as NLD when FVC maneuvers were used in isolation, 17 were reclassified when FVC and SVC maneuvers were used in combination. Of the 28 spirometry results interpreted as OLD with reduced FVC when FVC maneuvers were used in isolation, 8 were reclassified as OLD when FVC and SVC maneuvers were used in combination. Of the 91 cases that were diagnosed as OLD when FVC and SVC maneuvers were used in combination, only 54 had been diagnosed as OLD when FVC maneuvers were used in isolation. When normal spirometry results were excluded from the analysis, the kappa statistic was lower (0.506).

Reports of improvement in wheezing after bronchodilator administration were more common in the ΔSVC-FVC

Table 1. General and functional characteristics of the sample as a whole and of the two study groups.[a]

Parameter	Total sample	Group		p
		ΔSVC-FVC < 200 mL	ΔSVC-FVC ≥ 200 mL	
	(n = 187)	(n = 126)	(n = 61)	
Male sex	61 (32.62)	33 (26.20)	28 (45.90)	0.007*
Female sex	126 (67.40)	93 (73.81)	33 (54.10)	
Age, years	59.01 ± 12.80	59.70 ± 13.11	57.61 ± 12.11	0.300*
Height, cm	159.90 ± 9.60	158.37 ± 9.23	163.00 ± 9.70	0.002*
Weight, kg	78.46 ± 18.48	76.25 ± 16.86	83.12 ± 20.90	0.017*
BMI, kg/m^2	30.45 ± 6.40	30.26 ± 6.20	30.85 ± 6.84	0.553*
Smoking history, pack-years	18.30 ± 27.20	16.17 ± 25.82	22.70 ± 29.60	0.110**
Dyspnea, mMRC scale score	1.0 [0.0-4.0]	1.0 [0.0-4.0]	1.0 [0.0-4.0]	0.570**
FVC, L	2.83 ± 0.91	2.73 ± 0.90	3.03 ± 0.90	0.035**
FVC, % predicted	84.72 ± 17.35	85.11 ± 17.67	83.90 ± 16.79	0.666*
FEV_1, L	2.02 ± 0.73	1.99 ± 0.71	2.08 ± 0.76	0.418*
FEV_1, % predicted	75.00 ± 18.94	76.56 ± 18.44	71.87 ± 19.58	0.116*
FEV_1/FVC	0.71 ± 0.12	0.73 ± 0.10	0.68 ± 0.12	0.017**
PEF, L/s	6.92 ± 5.00	6.97 ± 5.87	6.82 ± 2.33	0.587**
SVC, L	3.00 ± 0.94	2.83 ± 0.91	3.35 ± 0.92	< 0.001*
SVC, % predicted	89.20 ± 17.00	87.50 ± 17.06	92.70 ± 16.50	0.049*
IC, L	2.12 ± 0.63	2.05 ± 0.62	2.26 ± 0.63	0.034*
FEV_1/SVC	0.67 ± 0.11	0.70 ± 0.10	0.61 ± 0.11	< 0.001**
FRC, L	2.93 ± 0.94	2.79 ± 0.90	3.21 ± 0.97	0.002**
TLC, L	5.05 ± 1.27	4.84 ± 1.22	5.47 ± 1.27	0.001**
TLC, % predicted	94.44 ±16.70	93.73 ± 16.86	95.92 ± 16.34	0.402*
RV, L	2.05 ± 0.79	2.01 ± 0.76	2.12 ± 0.86	0.185**
RV, % predicted	127.34 ± 45.00	129.17 ± 43.61	123.54 ± 47.90	0.424*
RV/TLC	0.41 ± 0.12	0.42 ± 0.11	0.39 ± 0.12	0.086*
IC/TLC	0.42 ± 0.10	0.43 ± 0.09	0.42 ± 0.09	0.495*
sGaw, L/s/cmH_2O	0.12 ± 0.08	0.12 ± 0.08	0.11 ± 0.07	0.380**
FRV, L	2.22 ± 0.81	2.11 ± 0.76	2.44 ± 0.85	0.02**
FRV, % predicted	155.71± 41.00	152.00 ± 36.51	163.84 ± 48.26	0.059*
ΔSVC-FVC, L	0.17 ± 0.14	0.095 ± 0.052	0.321 ± 0.132	< 0.001*

ΔSVC-FVC: difference between slow VC and FVC; BMI: body mass index; mMRC: modified Medical Research Council; SVC: slow vital capacity; FRC: functional residual capacity; IC: inspiratory capacity; sGaw: specific airway conductance; and FRV: forced residual volume. [a]Values expressed as n (%), mean ± SD, or median [minimum-maximum]. *Student's t-test. **Mann-Whitney U test.

Table 2. Agreement between the spirometry results obtained with FVC maneuvers alone and those obtained with FVC and slow vital capacity maneuvers in combination.[a,b]

Functional diagnosis		FVC + SVC maneuvers				Total	kappa	p
		Normal	OLD	OLD with reduced VC	NLD			
FVC maneuvers	Normal	52	21	0	0	73	0.653	< 0.001
	OLD	0	54	0	0	54		
	OLD with reduced FVC	0	8	20	0	28		
	NLD	4	8	5	15	32		
	Total	56	91	25	15	187		

SVC: slow vital capacity; OLD: obstructive lung disease; and NLD: nonspecific lung disease. [a]Values expressed as n. [b]Values in bold indicate diagnoses that were the same regardless of the diagnostic method used.

≥ 200 group than in the ΔSVC-FVC < 200 group (p = 0.04), as assessed by the aforementioned respiratory questionnaire.[11] Of the 17 participants with a history of tuberculosis, only 1 was in the ΔSVC-FVC ≥ 200 group (p = 0.011). There were no significant differences between the two groups regarding clinical diagnosis (Table 3).

The use of Pearson's or Spearman's correlation coefficient (data not shown) showed that ΔSVC-FVC correlated positively with height, FVC (L), SVC (L), SVC (% predicted), IC (L), TLC (L), and FRV (% predicted), as well as correlating negatively with FEV_1/(F)VC, RV (% predicted), and RV/TLC.

Table 3. Clinical diagnoses based on a < 200 mL difference between slow VC and FVC in comparison with those based on a ≥ 200 mL difference between slow VC and FVC.

Diagnosis	ΔSVC-FVC < 200 mL (n = 126)		ΔSVC-FVC ≥ 200 mL (n = 61)		p*
	n	%	n	%	
Unknown	33	26.20	16	26.23	0.566
Asthma	31	24.40	14	23.00	
COPD	15	11.80	10	16.40	
ILD	17	13.40	7	11.50	
Rhinitis	6	4.70	1	1.60	
Bronchiolitis	7	5.50	3	4.90	
Asthma + other	5	3.90	1	1.60	
COPD + other	0	0.00	2	3.30	
Other	12	9.40	7	11.50	

ΔSVC-FVC: difference between slow VC and FVC; and ILD: interstitial lung disease. *Fisher's exact test.

Table 4. Evaluation of demographic parameters (initial model) and functional parameters (final model) predicting a ≥ 200 mL difference between slow VC and FVC by logistic regression.

Initial model		
Demographic parameter	OR (95% CI)	p
Age, years	1.348 (0.501-3.629)	0.554
Female sex	0.774 (0.318-1.883)	0.572
Height, cm	1.016 (0.947-1.090)	0.655
Weight, kg	1.036 (0.983-1.091)	0.183
BMI, kg/m^2	1.038 (0.887-1.215)	0.644
BMI > 30 kg/m^2	5.075 (1.583-16.270)	0.006
Final model		
Functional parameter	Crude OR (95% CI)	Adjusted OR (95% CI)
FVC, L	1.425 (1.015-2.002)	1.020 (0.687-1.513)
FVC, % predicted	0.996 (0.979-1.014)	0.992 (0.974-1.011)
FEV_1, L	1.190 (0.782-1.812)	0.711 (0.426-1.188)
FEV_1, % predicted	0.987 (0.971-1.003)	0.980 (0.962-0.998)
FEV_1/FVC	0.967 (0.940-0.994)	0.952 (0.922-0.983)
SVC, L	1.831 (1.296-2.586)	1.399 (0.951-2.058)
SVC, % predicted	1.019 (1.000-1.038)	1.018 (0.997-1.038)
IC, L	1.695 (1.035-2.776)	1.014 (0.557-1.845)
FEV_1/SVC	0.931 (0.902-0.960)	0.908 (0.875-0.943)
TLC, L	1.492 (1.156-1.924)	1.282 (0.895-1.685)
TLC, % predicted	1.008 (0.989-1.027)	1.016 (0.995-1.037)
RV, L	1.188 (0.811-1.742)	1.201 (0.806-1.790)
RV, % predicted	0.997 (0.990-1.004)	1.002 (0.994-1.009)
RV/TLC	0.099 (0.007-1.400)	0.561 (0.030-10.561)
FRC, L	1.614 (1.155-2.255)	1.532 (1.063-2.808)
sGaw, cmH_2O/L/s	0.143 (0.003-8.005)	0.032 (0.000-3.000)
IC/TLC	0.988 (0.955-1.022)	0.956 (0.917-0.998)
FRV, L	1.692 (1.142-2.505)	1.697 (1.119-2.572)
FRV, % predicted	1.007 (1.000-1.015)	1.000 (0.992-1.009)
OLD_{FVC}	1.677 (0.906-3.107)	1.879 (0.948-3.723)
OLD_{SVC}	5.597 (2.543-12.322)	9.444 (3.708-24.049)
OLD_{PLET}	2.250 (1.151-4.397)	3.225 (1.497-6.948)

BMI: body mass index; SVC: slow vital capacity; IC: inspiratory capacity; FRC: functional residual capacity; sGaw: specific airway conductance; FRV: forced residual volume; OLD: obstructive lung disease; PLET: plethysmography.

As can be seen in Table 4, binomial logistic regression showed that weight and BMI > 30 kg/m^2 were predictors of a ΔSVC-FVC ≥ 200 mL (p < 0.20). Crude and adjusted ORs were calculated for weight and BMI > 30 kg/m^2 by means of a logistic regression analysis to evaluate spirometric and plethysmographic parameters. Reduced FEV_1 (% predicted), FEV_1/FVC, FEV_1/SVC, and IC/TLC, as well as increased FRC (L) and FRV (L),

Table 5. Multiple logistic regression analysis of bronchodilator response for a ≥ 200 mL difference between slow VC and FVC.[a]

Parameter	OR	95% CI	Pseudo r^2	p
FEV_1	4.38	1.45-13.26	0.112	0.009
FVC	3.83	1.26-11.71	0.090	0.018
SVC	0.63	0.38-4.91	0.040	0.630
IC	2.14	0.53-8.64	0.018	0.284
Any parameter responding positively	4.74	1.65-13.56	0.136	0.040

SVC: slow vital capacity; and IC: inspiratory capacity. [a]In comparison with a < 200 mL difference.

were independent predictors of a ΔSVC-FVC ≥ 200 mL. Increased SVC, IC, and TLC were associated with a ΔSVC-FVC ≥ 200 mL, albeit only in the crude model. OLD (characterized by reduced FEV_1/SVC, reduced sGaw, or a combination of the two) was independently associated with a ΔSVC-FVC ≥ 200 mL.

As can be seen in Table 5, our multiple logistic regression model showed that individuals with a ΔSVC-FVC ≥ 200 mL were more likely to show a significant change in FEV_1 (OR = 4.38; 95% CI: 1.45-13.26) and FVC (OR = 3.83; 95% CI: 1.26-11.71) than were those with a ΔSVC-FVC < 200 mL. However, in cases in which spirometry results were indicative of NLD or of OLD with reduced FVC and a significant bronchodilator response, a ΔSVC-FVC ≥ 200 mL failed to predict normal TLC (OR = 1.705; 95% CI: 0.333-8.721).

DISCUSSION

The use of SVC and FEV_1/SVC in the present study reduced the prevalence of NLD and of normal spirometry results by revealing airflow obstruction that can go unnoticed when only FVC and FEV_1/FVC are analyzed. Reductions in percent predicted FEV_1 and in FEV_1/(F)VC, as well as the presence of OLD, together with findings suggestive of air trapping (increased FRC and reduced IC/TLC),[24] were factors independently associated with a ΔSVC-FVC ≥ 200 mL. A significant bronchodilator response was more likely to occur in cases in which the ΔSVC-FVC was ≥ 200 mL.

In the present study, the spirometry results obtained with the combined use of FVC and SVC maneuvers changed the functional diagnosis that had been established with the use of FVC maneuvers alone. Of the 73 patients whose spirometry results were normal when FVC maneuvers were used in isolation, 21 were diagnosed with OLD when FVC and SVC maneuvers were used in combination. It has been reported that the prevalence of COPD in patients with mild disease is higher when assessed by FEV_1/SVC than when assessed by FEV_1/FVC.[25] Therefore, the FEV_1/SVC ratio plays an important role in revealing airflow limitation in smokers with respiratory symptoms and impaired quality of life presenting with normal FEV_1/FVC, thus contributing to an early diagnosis of COPD. However, in the present study, a ΔSVC-FVC ≥ 200 mL was found to be independent of the severity of OLD, a finding that is inconsistent with those of other studies.[4,5]

The use of SVC maneuvers in combination with FVC maneuvers changed the results of spirometry in 8 of 28 cases of OLD with reduced FVC (those 8 being reclassified as cases of OLD) and in 12 of 32 cases of NLD (those 12 being reclassified as normal cases [n = 4] or as cases of OLD [n = 8]). VC accounts for approximately 75% of TLC.[19] A finding of normal SVC is important because it can prevent the need for plethysmography in selected cases (given the difficulty of access to the test and the associated health care costs), especially in those in which a diagnosis of restrictive lung disease is less likely. However, a ΔSVC-FVC ≥ 200 mL failed to predict normal TLC in our sample.

In our initial logistic regression model, weight and a BMI > 30 kg/m^2 were predictors of a ΔSVC-FVC ≥ 200 mL. The association between weight and ΔSVC-FVC might be due to premature airway closure, given that there was no association with sGaw. Data from a large study suggest that ΔSVC-FVC is proportional to the increase in BMI, suggesting that obesity reduces FVC more than it does SVC; in contrast, in individuals with normal BMI and without OLD, SVC can be lower than FVC.[10]

Wang et al.[26] divided their study sample into two groups, namely those with SVC = FVC and those with SVC > FVC, and found that 65% of the sample had SVC > FVC, a finding that was more common in older individuals. In the present study, age was not associated with ΔSVC-FVC; however, the mean age of our sample was considerably high (i.e., 59 years), and it was impossible to establish a comparison with younger individuals.

Lung volumes (TLC, FRC, SVC, and IC) were predictors of a ΔSVC-FVC ≥ 200 mL, although only in the crude logistic regression analysis. Markers of airflow limitation (reduced FEV_1/FVC and FEV_1/SVC) and findings of air trapping (such as increased FRC and reduced IC/TLC)[24] were independent predictors of a ΔSVC-FVC ≥ 200 mL.

The magnitude of ΔSVC-FVC correlated negatively with RV and positively with FRV. This was confirmed by our logistic regression model, in which FRV (although not RV) was independently associated with the probability of a ΔSVC-FVC ≥ 200 mL. This might be due to the fact that measured VC is higher during a SVC maneuver because of reduced thoracic gas compression, leading to reduced RV if we assume that TLC remains unchanged. Conversely, during a FVC maneuver, increased thoracic gas compression can result in airflow limitation, leading to reduced FVC and, consequently, increased FRV.

Multiple logistic regression analysis showed that improvements in FEV_1 and FVC after bronchodilator administration were more common in the ΔSVC-FVC ≥ 200 group than in the ΔSVC-FVC < 200 group. This raises the question of whether significant or nonsignificant bronchodilator response can differentiate between true obstruction and a variant of normality, respectively, in individuals with an isolated finding of ΔSVC-FVC ≥ 200 mL. In the present study, no association was found between ΔSVC-FVC and OLD or restrictive lung disease/NLD.

The present study has some limitations. Strict inclusion criteria resulted in a limited sample size. In addition, there was no control group (comprising healthy individuals); most of the study sample consisted of diseased individuals.

Future studies should determine whether ΔSVC-FVC can predict exercise-induced hyperinflation and its association with the small airways (as assessed by imaging and biochemistry).

In conclusion, the use of an SVC maneuver appears to reduce the prevalence of NLD. Although it is possible that ΔSVC-FVC is due to airflow limitation and air trapping, it might be due to dynamic compression of the airways during exercise. Individuals with a ΔSVC-FVC ≥ 200 mL are more likely to have a significant bronchodilator response.

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Tumor-node-metastasis staging and treatment patterns of 73,167 patients with lung cancer in Brazil

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ABSTRACT

Objective: To characterize the clinical and histological profile, as well as treatment patterns, of patients with early-stage, locally advanced (LA), or advanced/metastatic (AM) lung cancer, diagnosed between 2000 and 2014, in Brazil. **Methods:** This was an analytical cross-sectional epidemiological study employing data obtained for the 2000-2014 period from the hospital cancer registries of two institutions in Brazil: the José Alencar Gomes da Silva National Cancer Institute, in the city of Rio de Janeiro; and the São Paulo Cancer Center Foundation, in the city of São Paulo. **Results:** We reviewed the data related to 73,167 patients with lung cancer. The proportions of patients with early-stage, LA, and AM lung cancer were 13.3%, 33.2%, and 53.4%, respectively. The patients with early-stage lung cancer were older and were most likely to receive a histological diagnosis of adenocarcinoma; the proportion of patients with early-stage lung cancer remained stable throughout the study period. In those with LA lung cancer, squamous cell carcinoma predominated, and the proportion of patients with LA lung cancer decreased significantly over the period analyzed. Those with AM lung cancer were younger and were most likely to have adenocarcinoma; the proportion of patients with AM lung cancer increased significantly during the study period. Small cell carcinoma accounted for 9.2% of all cases. In our patient sample, the main treatment modality was chemotherapy. **Conclusions:** It is noteworthy that the frequency of AM lung cancer increased significantly during the study period, whereas that of LA lung cancer decreased significantly and that of early-stage lung cancer remained stable. Cancer treatment patterns, by stage, were in accordance with international guidelines.

Keywords: Lung neoplasms/epidemiology; Lung neoplasms/therapy; Neoplasm staging; Brazil.

INTRODUCTION

Lung cancer (LC) is the most common cancer and the leading cause of cancer death worldwide. In 2012, there were over 1.8 million new cases and 1.6 million deaths worldwide.[1] For 2018, the *Instituto Nacional de Câncer José Alencar Gomes da Silva* (INCA, José Alencar Gomes da Silva National Cancer Institute) in Brazil estimates the occurrence of 31.270 new cases of trachea, bronchus, and LC: 18,740 in men and 12,530 in women. LC is the second most common cancer type among men and the fourth among women.[2]

The cancer staging system known as tumor-node-metastasis (TNM) determines the extent of disease by assessing the size of the primary tumor (T) and identifying whether there is any lymph node involvement (N) and local or distant metastasis (M). Cancers are usually classified as early-stage disease (stage I and II), locally advanced disease (stage III), and advanced/metastatic disease (stage IV). Staging is an important step in the diagnostic process, being aimed at standardizing the main treatment modalities for each stage, as well as at estimating prognosis and comparing the results of various therapies and therapy combinations and/or various institutions.[3,4]

The high mortality of LC and its low 5-year survival rate are attributable to the high prevalence of locally advanced and advanced/metastatic disease at diagnosis, observed in 70% to 95% of cases.[5,6] Clinically advanced/metastatic LC has recently been identified in 54.9% to 57.4% of cases at diagnosis and is on the rise in Brazil.[7,8] However, the other stages were not adequately assessed in those studies.[7,8]

Knowledge of the distribution of the clinical stages of LC is essential to optimizing smoking cessation programs, as well as cancer screening, diagnosis, and treatment at the national level, whether in the public or private sector.[9-12] Therefore, using data from hospital cancer registries, the present study aimed to characterize the clinical and histological profile, as well as treatment patterns, of patients with early-stage, locally advanced, or advanced/metastatic LC, diagnosed between 2000 and 2014, in Brazil.

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METHODS

This was an analytical cross-sectional epidemiological study employing data on adult patients with LC in Brazil, recorded between 2000 and 2014. Patient data were obtained from the records in the *Registro Hospitalar de Câncer* (RHC, Hospital Cancer Registry) Integration System of the INCA, located in the city of Rio de Janeiro, Brazil, and from the RHC of the São Paulo Cancer Center Foundation, located in the city of São Paulo, Brazil, which together involve 258 hospitals in 27 Brazilian states and the Federal District of Brasília.

The aforementioned systems were designed to store and consolidate data from all RHC in Brazil and can be consulted on the Internet. We included cases of malignant neoplasm of bronchus and lung, according to the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10 code C34),[13] with the following morphologies, according to the International Classification of Diseases for Oncology, 3rd edition[14]: adenocarcinoma (codes 8140, 8144, 8211, 8230, 8250, 8251, 8252, 8253, 8254, 8255, 8260, 8265, 8256, 8257, 8310, 8323, 8333, 8480, 8481, and 8551); squamous cell carcinoma (codes 8070, 8071, 8072, 8074, and 8083), small cell carcinoma (codes 8041 and 8045); and non-small cell carcinoma or undifferentiated carcinoma (code 8012). We excluded cases of patients who were under 18 years of age, had *in situ* carcinoma, or had lung tumors with other morphologies.

The 5th edition of the TNM classification was used in the 2000-2005 period; the 6th edition[13] was used in the 2006-2010 period; and the 7th edition[15] was used in the 2011-2014 period. Patients were categorized into three groups: early-stage group (ESG), patients with early-stage (stage I and II) LC; locally advanced group (LAG), patients with locally advanced (stage III) disease; and advanced/metastatic group (AMG), patients with advanced/metastatic (stage IV) disease. The following variables were categorized and analyzed: age group (18-49, 50-69, or ≥ 70 years); histological type[16] (adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma, or small cell carcinoma); smoking (never smoker or former smoker/smoker); race (White or Black/Brown); time from diagnosis to treatment initiation (< 60 days or ≥ 60 days); death at the end of the first treatment (yes or no); response to the first treatment (response [complete or partial response/stable disease] or no response [disease progression, recurrence, or death]); and first line of treatment (surgery alone, surgery + radiotherapy, surgery + chemotherapy, surgery + chemotherapy + radiotherapy, chemotherapy + radiotherapy, surgery at some point, radiotherapy at some point, and chemotherapy at some point).

Statistical analysis

Data analysis was performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). Measures of central tendency and dispersion were calculated for continuous variables, and frequency distribution was calculated for categorical variables. We used the chi-square test to compare the frequencies of categorical variables, considering valid data. To determine annual variation, we calculated the coefficient of determination. Differences were considered significant if $p < 0.05$.

The present study was approved by the Research Ethics Committee of the Professor Fernando Figueira Institute of Integrative Medicine (Protocol no. 3681 of 2013).

RESULTS

According to the RHC data, there were 103,658 cases of LC during the study period. A total of 30,491 records (29.4%) were excluded from the analysis because of missing data on TNM stage. Therefore, the study included 73,167 cases of patients diagnosed with LC between 2000 and 2014 in Brazil.

The main sociodemographic, clinical, and disease course characteristics of the cases, by stage, are shown in Table 1. There were 9,644 patients (13.2%) in the ESG; 24,511 (33.5%) in the LAG; and 39,012 (53.3%) in the AMG.

An analysis of the distribution of all early-stage, locally advanced, and advanced/metastatic LC cases between 2000 and 2014, by year of diagnosis, showed that relative frequency remained stable, trending slightly downward, in the ESG; decreased significantly in the LAG; and increased progressively and significantly in the AMG.

The mean age of the entire study sample was 63.5 ± 10.7 years, and 18% of the patients were never smokers (Table 1). There was a progressive increase in mean age at diagnosis in the three groups studied (Figure 1).

Patients with non-small cell carcinoma accounted for 90.8% of the sample, and this proportion trended slightly upward over the years evaluated. Patients with small cell carcinoma accounted for 9.2% of the sample, and their temporal distribution was opposite, trending slightly downward over the same period. Adenocarcinoma was the most common histological type (in 39.8%), followed by squamous cell carcinoma (in 29.0%) and undifferentiated carcinoma (in 22.1%; Table 1).

Chemotherapy was the most common treatment modality, in 59.4% of the patients, followed by radiotherapy (in 41.3%) and surgery (in 14.8%). No cancer treatment was administered to 10,766 patients (14.7%; Table 1).

In the ESG, the mean age was 64.8 ± 10.8 years, higher than that in the two other groups. Adenocarcinoma was the main histological type (in 42.3%), and the proportion of patients in whom the time from diagnosis to treatment initiation was ≥ 60 days (14.9%) was higher than that in the two other groups. The main treatment modality was surgery alone or in combination with other modalities (in 43.1%),

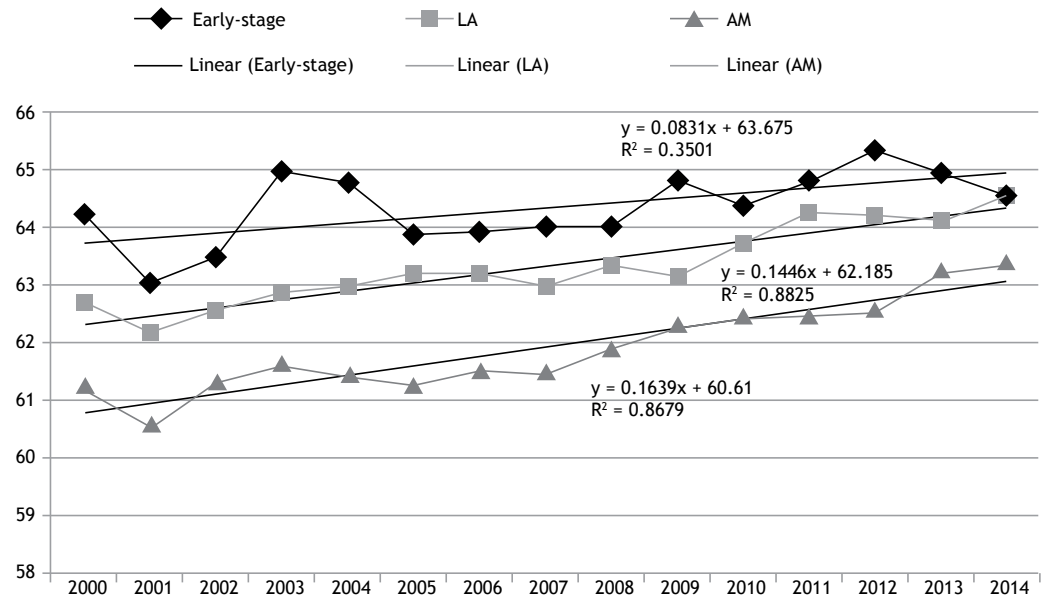

Figure 1. Distribution of all early-stage, locally advanced (LA), and advanced/metastatic (AM) lung cancer cases, by mean age and year of diagnosis, Brazil.

followed by chemotherapy (in 40.5%) and radiotherapy (in 32.2%). No treatment was administered in 10.8% of the cases. Death at the end of the first treatment occurred in 24.3% of the cases in the ESG. As shown by temporal analysis, the number of patients in the ESG remained stable throughout the period analyzed (Figure 2).

The LAG had the highest proportion of smokers (40.9%), and squamous cell carcinoma was the most common histological type at diagnosis; the proportion of patients with locally advanced LC decreased significantly during the study period (Figure 2). The main treatment modality was chemotherapy alone or in combination with other modalities (in 66.6%), followed by radiotherapy (in 48.7%) and surgery (in 16.8%). No treatment was administered in 11.8% of the cases (Table 1).

In the AMG, the mean age was lower than that in the two other groups. As shown by temporal analysis, advanced/metastatic LC was the most prevalent stage of LC in our patient sample, and the proportion of patients with advanced/metastatic LC increased significantly over the period analyzed. Adenocarcinoma was the predominant histological type (in 45.3%), and the proportion of patients in whom the time from diagnosis to cancer treatment initiation was ≥ 60 days was lower than that in the two other groups. The main treatment modality was chemotherapy (in 59.7%), followed by radiotherapy (in 38.9%) and surgery (in 12.6%). No treatment was administered to 17.4% of the patients. The AMG had the highest proportion of deaths at the end of the first treatment (47.4%).

The proportion of patients with adenocarcinoma trended upward in the ESG and the AMG, whereas it decreased significantly in the LAG (Figure 3A). The proportion of patients with squamous cell carcinoma was highest in the LAG; however, because this proportion decreased in the LAG and increased in the AMG, the latter group surpassed the former in the proportion of such patients as of 2011 (Figure 3B). The proportion of patients with small cell carcinoma trended downward in the ESG and the LAG during the study period (Figure 3C).

DISCUSSION

The present study, which evaluated 73,167 patients with LC, diagnosed between 2000 and 2014, in Brazil, showed that the prevalence of locally advanced LC decreased significantly during the study period, whereas that of advanced/metastatic LC increased significantly and that of early-stage LC remained stable. It also showed that surgery was the main treatment modality in the ESG, whereas chemotherapy was the main treatment modality in the LAG and the AMG.

Small cell carcinoma was identified in 9.2% of all patients in the present study, a frequency similar to those reported in the literature (10-15%) for the world population,[17] and the frequency of small cell carcinoma trended slightly downward during the study period. This decline in prevalence could be explained by the high correlation between small cell carcinoma and smoking, the prevalence of which is decreasing in Brazil; however, the behavior of this histological subtype was much more stable than that of squamous cell carcinoma, also a subtype frequently related to smoking,[8] in terms of the magnitude of the decrease in prevalence. Adenocarcinoma already is the most prevalent histological subtype in Brazil[8] and many other countries, is less correlated with smoking,

Table 1. Characteristics of the 73,167 patients with lung cancer in the study. Brazil, 2000-2014.

Characteristic	ESG Stage I and II n (%)	LAG Stage III n (%)	AMG Stage IV n (%)	p*
Number of patients	9,644 (13.3)	24,511 (33.2)	39,012 (53.4)	
Age, years (mean ± SD)	64.8 ± 10.8	63.4 ± 10.5	62.2 ± 11.0	< 0.001
Age group, years				< 0.001
• 18-49	822 (8.5)	2,417 (9.9)	4,847 (12.4)	
• 50-69	5,412 (56.1)	14,759 (60.2)	23,652 (60.6)	
• ≥ 70	3,410 (35.4)	7,335 (29.9)	10,513 (26.9)	
Gender				< 0.001
• Male	5,988 (62.1)	16,541 (67.5)	24,367 (62.5)	
• Female	3,656 (37.9)	7,970 (32.5)	14,645 (37.5)	
Race[a]				< 0.001
• White	3,051 (31.6)	8.852 (36.1)	12,812 (32.8)	
• Black/Brown	1,408 (14.6)	5,199 (21.2)	7,845 (20.1)	
• No data	4.735 (49.1)	10,460 (42.7)	20,657 (47.1)	
Smoking[a]				< 0.001
• No smoker	587 (6.1)	1,715 (7.0)	3,342 (8.5)	
• Smoker/former smoker	3,006 (31.1)	10,030 (40.9)	13,109 (33.6)	
• No data	6,266 (62.7)	13,026 (52.1)	23,264 (57.8)	
Histology				< 0.001
• Adenocarcinoma	4,079 (42.3)	7,373 (30.1)	17,658 (45.3)	
• Squamous cell carcinoma	3,413 (35.4)	9,701 (39.6)	8,095 (20.8)	
• Undifferentiated carcinoma	1,629 (16.9)	5,323 (21.7)	9,193 (23.6)	
• Small cell carcinoma	523 (5.4)	2,114 (8.6)	4,066 (10.4)	
Time from diagnosis to treatment initiation				< 0.001
• < 60 days	3,231(33.5)	11,613 (47.4)	18,299 (46.9)	
• ≥ 60 days	1,440 (14.9)	3,221 (13.1)	4,510 (11.6)	
No data	5,185 (51.6)	9,851 (39.5)	16,649 (41.5)	
First line of treatment				< 0.001
• No treatment	1,043 (10.8)	2,906 (11.9)	6,817 (17.5)	
• Surgery alone	943 (9.7)	384 (1.6)	597 (1.5)	
• Surgery + radiotherapy	590 (6.1)	1,076 (4.4)	1,452 (3.7)	
• Surgery + chemotherapy	1,418 (14.7)	1,835 (7.5)	2,233 (5.7)	
• Surgery + chemotherapy + radiotherapy	355 (3.7)	811 (3.3)	1,002 (2.6)	
• Chemotherapy + radiotherapy	1,349 (14.0)	7,762 (31.7)	8,488 (21.7)	
• Surgery at some point	4,153 (43.1)	2,809 (11.5)	3,832 (9.8)	
• Chemotherapy at some point	3,940 (40.5)	16,303 (66.6)	23,205 (59.7)	
• Radiotherapy at some point	3,103 (32.2)	11,958 (48.8)	15,213 (39.0)	
Response to the first treatment[a]				< 0.001
• Response[b]	1,751 (18.1)	3,629 (14.8)	3,082 (7.9)	
• No response[b]	1,115 (11.5)	5,853 (23.9)	10,431(26.7)	
• No data	6,778 (70.3)	15,029 (61.3)	25,499 (65.4)	
Early death[c]				< 0.001
• Yes	2,348 (24.3)	9,149 (37.3)	18,446 (47.3)	

Source: Hospital Cancer Registry Integration System of the *Instituto Nacional do Câncer* (INCA, National Cancer Institute) and Hospital Cancer Registries of the *Fundação Oncocentro de São Paulo* (FOSP, São Paulo Cancer Center Foundation). ESG: early-stage group; LAG: locally advanced group; and AMG: advanced/metastatic group. [a]Data not evaluated for the state of São Paulo (n = 34,181). Percentages based on valid data. [b]Response: complete or partial response, stable disease; and No response: progression, recurrence, or death. [c]Deaths at the end of the first treatment (INCA) or within 24 months after diagnosis (FOSP). *Chi-square test.

and trends toward a global increase in prevalence as compared with the other subtypes.[18-20]

In the present study, the proportional distribution of poor-prognosis stages is alarming but is similar to that found in the United States and the United Kingdom. Analyzing the mean proportions for each year during the study period (2000-2014), we found that early-stage LC, locally advanced LC, and advanced/metastatic LC

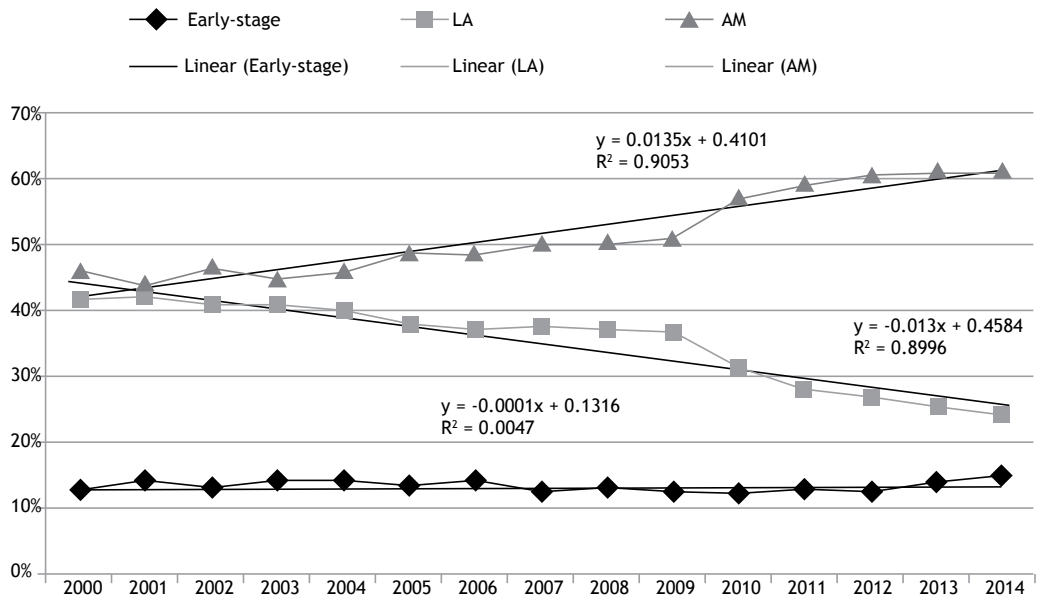

Figure 2. Distribution of all early-stage, locally advanced (LA), and advanced/metastatic (AM) lung cancer cases, by year of diagnosis, Brazil.

accounted for 13.3%, 33.2%, and 53.4% of the cases, respectively. In the United States, the proportions of early-stage, locally advanced, and advanced/metastatic LC cases were 15.9%, 22.0%, and 57.0%, respectively, in the 2008-2014 period.[21] In the United Kingdom, LC is the second most common cancer type in men and women, patients are diagnosed at stages III and IV in 87% of cases, and approximately 35% of cases are diagnosed after an emergency department visit.[22]

Further revisions to the TNM staging system[11] and histological classifications[17] and the implementation and greater availability of new technologies for the diagnosis of metastatic lesions, as well as the increase in the number of cancer treatment centers in recent years, are possibly the main factors related to the increased proportion of LC cases diagnosed at an advanced stage in Brazil. The Expand project, developed by the Brazilian National Ministry of Health in conjunction with the INCA, has created 24 new oncology centers since 2000.[23] Positron-emission tomography is a new diagnostic technology that combines nuclear medicine and tomography, being more reliable and precise in staging LC when compared with tomography alone, as well as reducing futile treatments for patients and reducing costs to the health care system.[24]

The National Lung Screening Trial[25] established that low-dose chest CT, repeated annually for 3 years when used for the screening of asymptomatic high-risk patients (age > 55 years, smokers with a smoking history > 30 pack-years, and former smokers who have been abstinent for less than 15 years), increases survival in those with positive screening for LC, with a reduction of 20% in LC mortality and of almost 7% in all-cancer mortality. A study of LC screening, conducted in Brazil,[26] evaluated 790 high-risk patients and identified 312 (39.4%) with nodules > 4 mm; those 312 patients were followed by a multidisciplinary team. A total of 10 cases (3.2%) of LC were found, suggesting that low-dose CT can and should be even used in a region with a high incidence of granulomatous diseases. In addition to identifying nodular lesions suspected of being LC, CT offers the benefit of incidental findings of other diseases, such as benign lung diseases (COPD, interstitial diseases, and bronchiectasis) and cardiovascular diseases (based on the degree of coronary artery calcification), at earlier stages; such findings are present in 24% to 64% of cases.[27] However, LC screening is not yet available in Brazil via the Brazilian Unified Health Care System. Brazilian National Ministry of Health Directive no. 600 issued on June 26, 2012,[28] which approved diagnostic and treatment guidelines for LC, does not recommend the routine use of low-dose chest CT for this purpose.

Although Brazil is a worldwide reference in the fight against smoking, centers specializing in smoking cessation have yet to expand their actions.[29] The prevention-related costs of smoking cessation programs are infinitely lower than the exorbitant costs of medical and hospital care for smoking-related diseases. In 2011, a study conducted in Brazil reported that smoking was responsible for 147,072 deaths, 2.69 million years of life lost, 157,126 cases of acute myocardial infarction, 75,663 cases of stroke, and 63,753 cases of cancer. The total cost to the health care system was 23.37 billion Brazilian reals.[30] Combining screening programs with smoking cessation programs appears to be far more effective in reducing costs and mortality from LC and other causes.[25,31]

The training of primary and secondary health care professionals also needs to be optimized so that LC can be diagnosed as early as possible. Lista et al.[32] retrospectively evaluated 372 patients with LC who were

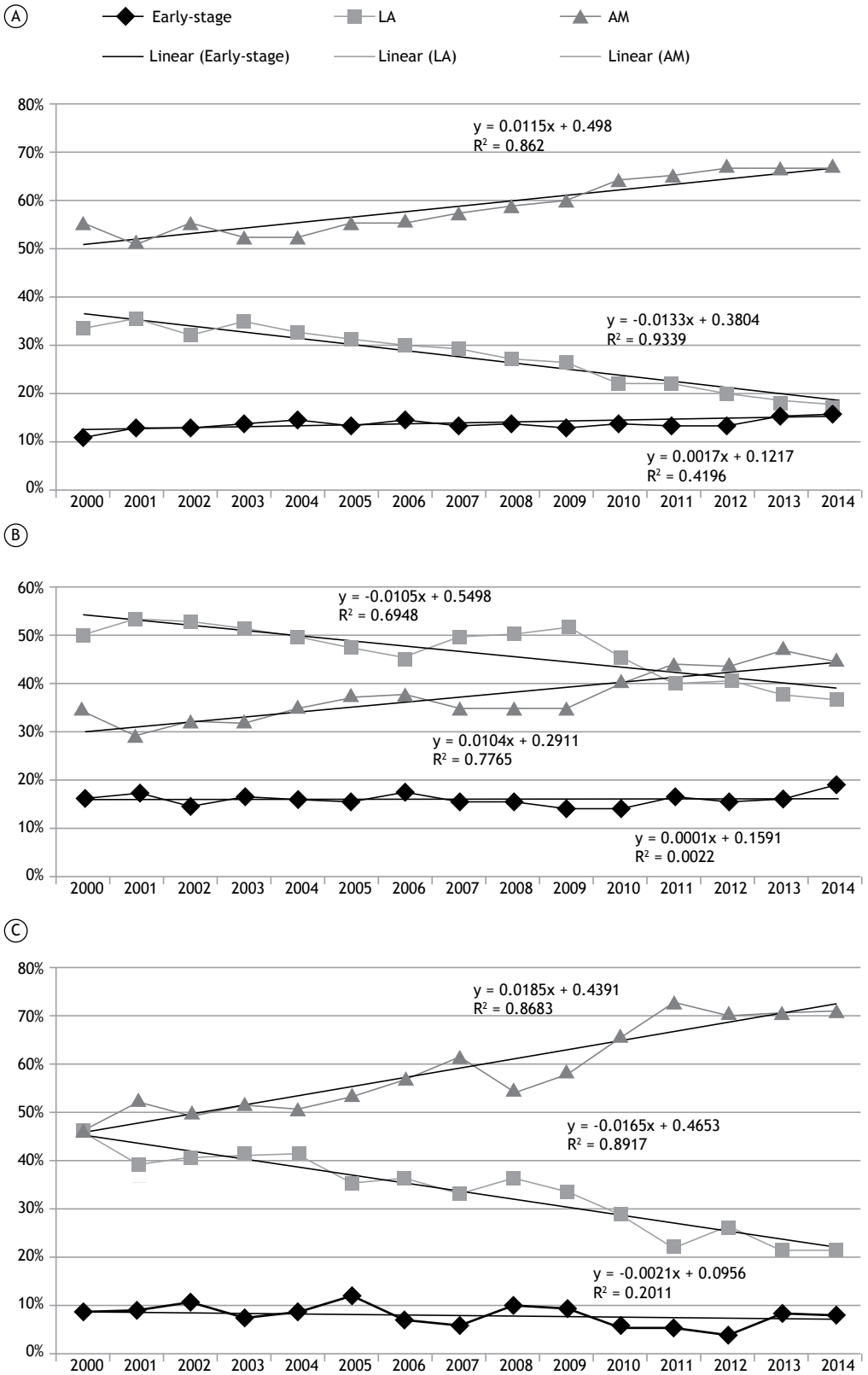

Figure 3. Distribution of all early-stage, locally advanced (LA), and advanced/metastatic (AM) lung cancer cases, by histology and year of diagnosis, Brazil. In A, adenocarcinoma. In B, squamous cell carcinoma. In C, small cell carcinoma.

treated at a cancer institute in Brazil and found that, in almost 80% of the first treatments, the diagnosis of LC was not considered and that only 6.8% of the patients were diagnosed with the disease less than 30 days after symptom onset. Those authors also reported that, in only 18.5% of the cases, the delayed diagnosis of LC was due to the patient; therefore, in Brazil, the physician/health care system is largely responsible for the delay in diagnosis in patients with LC.[32]

In the present study, 10% to 18% of all patients with LC did not receive any cancer treatment, regardless of disease stage. This is probably due to the poor clinical status of patients making them unable to bear the risks of treatment,[33] to patient personal preference not to be treated, or to delayed diagnosis.[32] More than 75% of patients depend exclusively on the Brazilian Unified Health Care System, which, despite being purposed for providing universal care, has numerous problems related to access,[34] delay in histological[32] or molecular[35] diagnosis, treatment availability, and the wide disparity among cancer care centers in terms of the technology available for diagnosis or treatment.[36] This situation in Brazil is similar to that in other Latin American countries, where the provision of care to patients with cancer is also precarious.[37]

Age is an independent risk factor for the development of cancer.[38] In the present study, we found that the mean age of the diagnosed patients is increasing, which characterizes an increasingly older population. In addition, almost 35% of patients with early-stage disease, who have the best cure rates, are over 70 years of age. However, this population is often undertreated from an oncologic standpoint,[8,37] although it may have good results.[39-41] It can be speculated that, because of their comorbidities, elderly patients seek health care services earlier[29] and can thus be diagnosed at earlier stages of the disease.

Overall, chemotherapy was the main treatment modality in the present study. It is the modality of choice for the systemic treatment of cancer.[33] Radiotherapy and surgery are regional treatment modalities. The latter is the mainstay of the treatment for patients with early stage LC, being used alone or in combination with chemotherapy in order to achieve better survival results.[42] Surgery was performed at some point in only 15% of the cases, but it was the main treatment modality at early stages.

The present study has some limitations, especially because we analyzed retrospective data obtained from RHC. It has problems regarding the level of completeness of the variables analyzed, as well as lacking data on molecular analysis, comorbidities, and objective assessment of patient functional performance. Finally, histological confirmation of cases was not possible, nor was review of stage data. However, the study was based on data from large nationwide databases that have a significant body of information about the epidemiological profile with an emphasis on disease staging and treatment patterns of patients with LC in Brazil, which were the object of this study.

To date, this has been the largest study analyzing TNM staging and treatment patterns of patients with LC in Brazil. The information gathered here may be valuable for understanding the current status of LC in Brazil and, consequently, for planning and implementing public health policies targeting LC patients in the country, such as combining screening programs with smoking cessation programs, training primary and secondary health care professionals to identify populations at increased risk, and identifying radiological lesions suspected of progressing to LC so that patients can be referred earlier to specialized health care facilities for diagnosis and treatment.

The present study showed that the frequency of stage III LC decreased significantly, a decrease characterized in part by a reduction in the frequency of the squamous cell carcinoma histological subtype, whereas the frequency of stage IV LC increased significantly and that of early-stage LC remained stable. In addition, our study showed that cancer treatment patterns, by clinical and/or pathological stage in patients with LC in Brazil, were in accordance with international guidelines.

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Reference values for the Unsupported Upper Limb Exercise test in healthy adults in Brazil

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ABSTRACT

Objective: To establish reference values for the Unsupported Upper Limb EXercise (UULEX) test, which measures peak arm exercise capacity, in healthy adults in Brazil. **Methods:** This was a cross-sectional study, involving presumably healthy individuals ≥ 30 years of age who completed questionnaires and underwent spirometry. All of the individuals underwent two UULEX tests 30-min apart. The outcome measure was the maximum time (in min) to completion of the test. **Results:** We included 100 individuals between 30 and 80 years of age. The mean test completion time was 11.99 ± 1.90 min among the women and 12.89 ± 2.15 min among the men ($p = 0.03$). The test completion time showed statistically significant correlations with age ($r = -0.48$; $p < 0.001$), gender ($r = 0.28$; $p = 0.004$), body mass index (BMI, $r = -0.20$; $p = 0.05$), and height ($r = 0.28$; $p = 0.005$). Linear regression analysis showed that the predictors of UULEX completion time were age ($p = 0.000$), BMI ($p = 0.003$), and gender ($p = 0.019$), which collectively explained 30% of the total variability. The mean UULEX completion time was 6% lower for the women than for the men. **Conclusions:** The present study was able to establish reference values for the UULEX test in healthy adults in Brazil. The values were influenced by age, gender, and BMI.

Keywords: Reference values; Exercise test; Upper extremity.

INTRODUCTION

Peripheral muscle dysfunction is one of the most common extrathoracic manifestations of COPD and has been associated with poor prognosis.[1] Studies have shown that a reduction in muscle mass and strength is a predictor of mortality[2,3] and a marker of exacerbation risk in COPD patients.[4] The cause of peripheral muscle dysfunction is multifactorial, the main factors involved being physical inactivity, malnutrition, exacerbations, and corticosteroid use.[5] Although leg muscles are more affected than are arm muscles,[5,6] COPD patients have great difficulty performing activities of daily living that involve the arms, especially those that involve unsupported arms. During such activities, there is an increase in oxygen consumption and greater use of the ventilatory reserve.[7] In addition, there is thoracoabdominal asynchrony, a decrease in inspiratory capacity,[6,8] and an increase in the levels of lactic acid, worsening the sensation of dyspnea.[9] Therefore, these individuals perform activities that involve the arms at a lower intensity compared with their healthy peers.[10]

Arm muscle training should be part of pulmonary rehabilitation programs.[11] Studies have shown an improvement in exercise capacity,[12,13] dyspnea,[14] and arm function[13] after a specific physical training program. A simple, inexpensive test that has been used to assess arm exercise capacity in clinical trials and rehabilitation programs is the Unsupported Upper Limb EXercise (UULEX) test.[15] The UULEX test is a standardized symptom-limited incremental test that assesses peak unsupported arm exercise capacity.[15] The movements made during the test reflect the arm movements made during daily tasks, which makes the test have great clinical application. This test is valid and reliable in COPD patients.[15,16]

The UULEX test has the potential to be used even in healthy individuals. No ceiling effect has been reported and test-retest reliability is good in this population.[17] Nevertheless, to date, no reference values have been

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established for the UULEX test in the Brazilian population. These values would help determine the degree of dysfunction and understand the problems related to activities of daily living that involve unsupported arms among individuals with COPD or other clinical conditions, such as orthopedic[18] or neurological[19] impairments. In addition, they would serve as parameters for assessment of response to pulmonary rehabilitation programs.

The objective of the present study was to establish reference values for the UULEX test in a sample of healthy adults in Brazil.

METHODS

This was an observational cross-sectional study conducted in the *Universidade Federal de Minas Gerais* (UFMG, Federal University of Minas Gerais) Department of Physical Therapy Laboratory for the Evaluation of and Research on Cardiopulmonary Performance, located in the city of Belo Horizonte, Brazil. Participants were recruited through posters, electronic messages, and advertisements targeting the internal and external community of the UFMG. The inclusion criteria were as follows: being between 30 and 89 years of age; having no history of chronic disease; having no limitation of shoulder or arm movements that might impair test performance; having no symptomatic heart or lung disease; having normal spirometry results; being able to read and speak Portuguese; and reporting being healthy (a healthy person was defined as one who can perform his or her activities of daily living without limitations).[20] The exclusion criteria were as follows: having recently undergone a surgical procedure that prevented him or her from undergoing the study protocol; having a history of smoking; or being over 65 years of age and having a Mini-Mental State Examination score below 13 (for those who were illiterate), below 18 (for those with a low or medium level of education) or below 26 (for those with a high level of education).[21]

The study was approved by the UFMG Research Ethics Committee (CAAE no. 47887415.6.0000.5149). All participants gave written informed consent.

Measurement instruments

Unsupported Upper Limb EXercise test

The UULEX test was performed as described by Takahashi et al.[15] To perform the test, the participant sat on a chair facing a board (120 cm in height × 84 cm in width) with eight 8-cm-wide color bands, which were 5 cm apart (Figure 1). The participant remained seated throughout the test. The first level was set at knee-height. The participant received a PVC tube weighing 0.2 kg. The test started with the participant warming up for 2 min, moving his or her arms from the pelvic girdle to the first level on the board, located at knee-height. After the warm-up period, the participant moved to the next level on the board (level 2), performing the same movement for 1 min. The level was changed every minute. When the maximum vertical height, that is, level 8 on the board, was reached, the 0.2-kg PVC tube was replaced by a 0.5-kg one and the participant should continue the exercise by moving the tube from the pelvic girdle to level 8 on the board, without stopping at the other levels, for 1 min. From this time point onward, the tube was replaced by a 0.5-kg heavier one every minute until a maximum of 2.0 kg was reached. The test was performed at a steady pace, at a metronome-controlled cadence of 30 bpm. Throughout the test, the participant was encouraged to continue the exercise as long as possible until exhaustion. Participants were not allowed

Figure 1. Volunteer performing the test.

to stop during the test; if this happened, the test was ended. The test interruption criteria were as follows: requesting to stop the test; not performing the full arc of motion; or being unable to keep up with the metronome pace. The maximum test duration was 15 min; if the volunteer completed 15 min of test, the test was ended. This value was chosen because the mean test duration was 14.21 min in a previous study of healthy individuals.[22] The outcome measure was the maximum time (in min) to completion of the test, that is, a longer time equals a better result.

Human Activity Profile

The Human Activity Profile (HAP) instrument has been cross-culturally adapted for use in Brazil.[23] The HAP is used to assess the level of physical activity in both healthy individuals and individuals with a medical condition. It consists of 94 items presented in ascending numerical order, from the lowest energy expenditure activity (1) to the highest energy expenditure activity (94). For each item, there are three possible answers: "I am currently able to perform the activity"; "I have stopped performing the activity"; or "I have never performed the activity". From the answers given, a maximal activity score (MAS) is derived, representing the highest oxygen-demanding activity that the individual is still able to perform. Then, an adjusted activity score (AAS) is calculated by subtracting from the MAS the number of activities with lower energy requirements that the individual has stopped performing. According to the AAS, the participants were classified as inactive (AAS < 53 points), moderately active (53 ≤ AAS ≤ 74), or active (AAS > 74).[23]

Body mass index

The body mass index (BMI) was calculated by the formula weight (kg)/height^2 (m^2). Weight was measured with an anthropometric scale (Filizola, São Paulo, Brazil). Height was measured with the scale's stadiometer. For this measurement, participants were placed in a standing position, barefoot, with the feet parallel, the heels together, and the arms hanging at the sides. The head was positioned so that the lower part of the eye socket was in the same plane as the outer ear hole. On the basis of the results, participants were classified in accordance with the Brazilian Guidelines for the Management of Obesity.[24]

Pulmonary function

Pulmonary function was assessed by spirometry (Koko spirometer; PDS Instrumentation Inc., Louisville, CO, USA). Spirometric measurements were performed by a qualified technician, in accordance with the American Thoracic Society standards.[25] FVC and FEV_1 were calculated from the flow-volume curve and were expressed as absolute values (in L) and as a percentage of predicted values. The FEV_1/FVC ratio was also recorded. The reference values used were those for the Brazilian population.[26]

Procedures

Participants were evaluated on a single day. After written informed consent was obtained, demographic data, including gender, age, and anthropometric measurements, were collected. Participants were then administered the PAH questionnaire. Subsequently, to ensure that participants did not have lung disease, they underwent spirometry. After a 10-min rest period, the test session was started. All participants underwent two UULEX tests 30 min apart.

Statistical analysis

Sample size was calculated as recommended by Ceriotti et al.[27]

Data are presented as means and standard deviations. Continuous variables were assessed for normality of distribution with the Shapiro-Wilk test. Bivariate associations were assessed with Pearson's correlation test. Variables were selected for inclusion in the multiple linear regression model on the basis of correlation analysis. A value of $p < 0.05$ was used as the criterion for including a variable, and a value of $p > 0.10$ was used as the criterion for excluding it. The multiple linear regression model was built in a stepwise fashion. The final model was determined by the adjusted coefficient of determination (r^2) and by statistical significance. The existence of multicollinearity was analyzed using variance inflation factors (> 0.2) and tolerance (< 5), and the distribution of residuals was tested for normality using Q-Q plots. To determine the lower limit of normal (LLN), the following formula was devised:

LLN = value predicted by the linear regression equation − (1.64 × *standard error of the estimate*)

The level of significance was set at $p < 0.05$. Statistical analyses were performed with the IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

We included 100 individuals in the study, 52 of whom were male. The mean age was 55.87 ± 14.67 years, and the mean BMI was 26.59 ± 3.75 kg/m^2. All participants had normal pulmonary function. The spirometric values expressed as a percentage of predicted values were as follows: FVC = 95.12 ± 12.74%; FEV_1 = 94.38 ± 13.51%; and FEV_1/FVC ratio = 96.69 ± 8.30%. Seventy percent of the participants were classified as active by the PAH. Table 1 shows the anthropometric and demographic characteristics of the participants by gender and age group.

The mean UULEX completion time was 11.99 ± 1.90 min among the women and 12.89 ± 2.15 min among the men ($p = 0.03$); that is, the mean test completion time was 6% lower for the women than for the men. The test completion time showed statistically significant correlations with age ($r = -0.48$; $p < 0.001$), gender ($r = 0.28$; $p = 0.004$), BMI ($r = -0.20$; $p = 0.05$),

and height (r = 0.28; p = 0.005) but not with weight (r = 0.08; p = 0.41) or level of physical activity (r = 0.12; p = 0.22). Linear regression analysis of the observed correlations showed that the predictors of UULEX completion time were age (p < 0.001), BMI (p = 0.003), and gender (p = 0.019), which collectively explained 30% of the total variability (r^2 = 0.30; p < 0.005).

UULEX (time in min) = 1,079.96 + (43.531 × [0 woman; 1 man]) − (2.96 × *age*) − (7.45 × *BMI*)

Table 2 shows the mean, minimum, and maximum time (in min) to completion of the UULEX test in the sample by gender.

DISCUSSION

This was the first study to establish reference values for the UULEX test in individuals over 30 years of age in Brazil.

Our results show a negative relationship between test completion time and age. Younger individuals had better test results. Lima et al.,[28] in a study of 104 healthy individuals over 30 years of age, presented reference values for another test that assesses arm endurance and reported that age was the sole determinant of better performance. Another study assessed arm functional capacity in adults and elderly individuals and showed a negative association between age and test performance.[29] Aging is known to be accompanied by declines in bodily functioning, the most important of which is loss of muscle mass and strength.[9] These declines start around age 30, and there is an estimated annual loss of muscle mass of 0.1-0.5% after this age.[30] These factors may explain the findings of the present study.

Another variable that showed a negative relationship with test completion time was BMI. Previous studies on reference values for other tests that assess functional capacity have reported this association.[31,32] However, a study that assessed arm function using the six-minute pegboard and ring test, the purpose of which is to move as many rings as possible in 6 min, found no correlation between test performance and BMI.[33] These findings differ from those in the present study; however, we should take into consideration that the sample of that study was younger (mean age of 23.41 ± 3.58 years among the men and 23.27 ± 3.0 years among the women) and had a lower BMI (25.09 ± 3.91 kg/m^2 among the men and 22.26 ± 2.36 kg/m^2 among the women), which may have affected the results. In the present study, the mean age overall was 55.87 ± 14.67 years, and the mean BMI was 26.59 ± 3.75 kg/m^2, classified as overweight.[24] Aging is accompanied by an increase in muscle fiber fat tissue and accumulation of subcutaneous fat, which is a negative predictor of muscle quality, as well as

Table 1. Anthropometric and demographic characteristics of the 100 participants by gender and age group.[a]

Gender Age group, years	n	Age, years	Height, m	Weight, kg	BMI, kg/m^2	AAS
Women						
31-40	8	33.00 ± 2.64	1.69 ± 0.08	69.62 ± 6.74	24.51 ± 3.46	90.00 ± 3.43
41-50	10	46.70 ± 2.62	1.63 ± 0.10	67.99 ± 11.09	25.39 ± 4.05	84.40 ± 8.27
51-60	9	54.67 ± 3.24	1.57 ± 0.44	66.00 ± 7.49	26.64 ± 3.08	75.11 ± 8.62
61-70	10	66.70 ± 2.26	1.55 ± 0.03	67.13 ± 10.21	27.69 ± 4.15	72.00 ± 10.70
71-80	11	76.00 ± 2.36	1.53 ± 0.07	69.23 ± 10.70	29.27 ± 3.65	73.73 ± 8.74
Men						
31-40	11	35.73 ± 2.61	1.82 ± 0.09	87.69 ± 11.18	26.44 ± 2.45	88.73 ± 6.73
41-50	11	46.18 ± 2.72	1.72 ± 0.05	81.30 ± 4.86	27.46 ± 1.87	89.91 ± 4.34
51-60	11	56.45 ± 3.26	1.71 ± 0.07	76.11 ± 10.90	26.03 ± 3.43	83.82 ± 9.33
61-70	9	65.00 ± 3.50	1.71 ± 0.08	75.07 ± 23.25	25.20 ± 6.20	78.78 ± 14.06
71-80	10	75.30 ± 2.16	1.71 ± 0.06	78.22 ± 14.53	26.40 ± 3.50	78.20 ± 8.23

BMI: body mass index; and AAS: adjusted activity score. [a]Values expressed as mean ± SD.

Table 2. Mean, minimum, and maximum time (in min) to completion of the Unsupported Upper Limb EXercise test by gender, as well as the lower limit of normal calculated using the regression model.

Age group, years	Women (n = 48)		Men (n = 52)	
	Time, min	LLN[a]	Time, min	LLN[a]
31-40	13.99 (12.20-15.00)	11.51	14.24 (13.19-15.00)	11.75
41-50	13.40 (12.15-15.00)	10.92	14.10 (10.32-15.00)	11.62
51-60	12.50 (9.48-15.00)	10.01	13.26 (9.00-15.00)	10.78
61-70	11.72 (9.36-13.20)	9.23	13.05 (9.00-15.00)	10.56
71-80	11.66 (9.01-13.51)	9.18	12.47 (8.17-15.00)	9.98

LLN: lower limit of normal. SEE: standard error of the estimate = 91.04. [a]LLN = mean test completion time − (1.64 × SEE). UULEX completion time (min) = 1,079.96 + (43.531 × [0 woman, 1 man]) − (2.96 × age) − (7.45 × body mass index). r^2 = 0.30.

by disturbances in muscle metabolism, leading to a decrease in oxidative capacity and capillary density in obese individuals, which explains poorer performance on the test with increasing BMI.[34]

Women performed more poorly compared with men in all age groups. On average, men performed 6% better. The UULEX test requires manual dexterity, motor coordination, and strength. According to the literature, manual dexterity and motor coordination are not associated with gender,[28] which indicates that strength may be responsible for the differences found in the present study. Men have greater muscle mass and a lower fat percentage and, consequently, more strength. In addition, men have more efficient aerobic and anaerobic energy production.[35]

The limitations of our study are related to the fact that we were unable to obtain a sample of individuals over 80 years of age, mainly because of the large number of comorbidities present in this age group that met the exclusion criteria. This may limit the external validity for this age group. In addition, the low r^2 value and the fact that the equation was not tested in an independent sample are limitations of the study. However, it is not uncommon to find low r^2 values in the literature on reference values.[32,36,37] To our knowledge, this is the first study involving a large sample of the Brazilian population that has sought to establish reference values for the UULEX test.

In conclusion, the present study was able to establish reference values for the UULEX test in a sample of healthy adults in Brazil. The reference values were influenced by age, gender, and BMI. These values will allow the identification of impairments in peak arm exercise capacity in people with different arm functional limitations. These data will be useful both in clinical practice, for measuring the results of pulmonary rehabilitation programs, and in the undertaking of clinical research in the area.

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Smoking among industrial workers in Brazil: association with sociodemographic factors, alcohol consumption, and stress levels

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ABSTRACT

Objective: To determine the prevalence of smoking, as well as its association with sociodemographic factors, alcohol consumption, and stress levels, among industrial workers in Brazil. **Methods:** This was a nationwide survey, conducted in 24 capitals in Brazil through the application of a pre-tested questionnaire. The response to the question "What is your smoking status?" was the outcome variable. To determine the associations, we performed Poisson regression analyses in which the inputs were blocks of variables: block 1 (age and marital status); block 2 (level of education and gross family income); block 3 (geographic region); and block 4 (alcohol consumption and stress level). All analyses were stratified by gender. **Results:** The sample consisted of 47,328 workers ≥ 18 years of age, of whom 14,577 (30.8%) were women. The prevalence of smoking was 13.0% (15.2% in men and 7.9% in women). Advancing age, alcohol consumption, and a high stress level were positively associated with smoking. A lower risk of smoking was associated with being married, having a higher level of education, and living in the northeastern region of the country (versus the southern region). **Conclusions:** The prevalence of smoking was greater in men than in women. Alcohol consumption and high stress levels appear to promote smoking.

Keywords: Tobacco use disorder/epidemiology; Tobacco smoking; Occupational health; Industry; Brazil.

INTRODUCTION

Smoking is an important risk factor for various morbidities and is associated with early onset of cardiovascular diseases, respiratory diseases, some types of cancer, stroke, and increased mortality.[1] Nevertheless, 928 million men and 207 million women smoke.[2]

In Brazil, data from a nationwide telephone survey demonstrated a decrease in the prevalence of smokers ≥ 18 years of age: from 15.6% in 2006 to 10.8% in 2014.[3] In 2017, this prevalence was close to 10%, being higher among men than among women (13.2% vs. 7.5%).[4] Therefore, smoking differs by sociodemographic factors, such as gender and economic status.[3,5] Studies have indicated that adult men[4] with a low family income and a low level of education[6] are more likely to smoke. In addition, certain risk conditions, such as alcohol consumption and stress levels, appear to be directly related to smoking.[7,8]

It remains unknown whether the behaviors seen in the general population manifest themselves in the same pattern among industrial workers, because the circumstances of this social group are known to be determined by social, economic, and organizational factors, as well as by working/living conditions and specific occupational risk factors.[9]

Surveillance of these various factors, in parallel with monitoring of smoking,[3,10,11] knowledge of the deleterious effects of smoking, and understanding of the importance of prevention[12] can potentiate the development and implementation of anti-smoking policies in the workplace, such as the 2011 Anti-Smoking Law.[13] These actions are aimed at reducing the health harms caused by and the more serious consequences of smoking, such as the onset of morbidities and early mortality attributable to tobacco use.[14]

Considering that industrial workers correspond to a specific class of Brazilian adult workers, who have different work routines, we sought to assess whether exposures to alcohol consumption and stressful situations are associated with smoking. Therefore, the objective of the present study was to determine the prevalence of smoking, as well as its association with sociodemographic factors, alcohol consumption, and stress levels, among industrial workers in Brazil.

METHODS

The present study is part of a nationwide survey entitled "Lifestyle and Leisure Habits of Industrial workers",[15]

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carried out by the Brazilian *Serviço Social da Indústria* (SESI, Industrial Social Services Agency) in partnership with the Federal University of Santa Catarina Center for Research on Physical Activity and Health, between 2006 and 2008, with the participation of 24 of the 27 federal units in Brazil. This was a representative study of Brazilian industrial workers in Brazilian capitals. The states of Rio de Janeiro, Piauí, and Sergipe did not participate in the survey in a timely manner.

In 2006, Brazil had approximately 5,293,000 industrial workers.[16] For the survey, each regional department of the SESI provided worker registration information and information on the number of workers at each company in the state it represented. Information on population size was provided by each regional department, and, on the basis of those data, we calculated the sample size using the following parameters: an estimated prevalence of leisure time physical inactivity of 45%, obtained from a survey conducted in Santa Catarina, the main purpose of which was to identify the prevalence of leisure time physical inactivity[17]; a sampling error of 3%; and a confidence interval of 95%. The minimum sample size was then increased by 50% as a strategy to attenuate the effects of the sampling design; subsequently, the sample size was increased by an additional 20% to account for potential losses during the data collection process.[15] The total sum of samples from all regional departments was 52,774 workers. The sampling plan was developed separately in each regional department, in two stages: random selection of companies, considering the distribution of workers in companies by company size—small (20-99 workers), medium (100-499 workers), and large (≥ 500 workers)—10-50% of small, medium, and large companies being selected depending on the number of existing companies and the required number of patients for the sample; and random selection (systematic sampling) of workers in each of the companies selected in the previous phase of the sampling process. The sampling plan was then sent to each regional department, so that the companies could be contacted and the questionnaires could be administered. Companies that did not allow the administration of the questionnaires were replaced with companies of the same size and, when possible, in the same industry. Workers who were absent or on leave were replaced by choosing the next name on the employee list provided by the company. More details can be found in a previous publication.[15]

The data in the present study were collected using a self-report questionnaire with 58 questions.[17] Content and logic validity were checked. Kappa index values and intraclass correlation coefficients ranged from 0.40 to 0.79.[17] For the present study, 9 items of the questionnaire were used: tobacco use ("What is your smoking status?"); alcohol consumption ("How many alcoholic drinks do you consume in a typical week?"); stress level ("How would you rate the stress level in your life?"); geographic region of the regional department of the SESI; gender; age; marital status (married/living with a partner or other); level of education; and gross family income. The ways in which data on the study variables were collected and operationalized can be seen in Chart 1.

We used relative frequencies to describe the study variables. We performed crude and adjusted Poisson regression analyses to determine the association of smoking with demographic profile, socioeconomic profile, alcohol consumption, and stress levels. In the adjusted model, the critical level of p for variable selection was set at $p \leq 0.05$, in order to control for possible confounding factors.

Variables were entered in blocks, according to the Dumith model,[18] in the following order: block 1 (age and marital status); block 2 (level of education and gross family income); block 3 (geographic region); and block 4 (alcohol consumption and stress level). In the adjusted analyses, the variables in the next block were adjusted for the variables in the previous blocks. All analyses were stratified by gender, and the level of statistical significance was set to 5% ($p < 0.05$). For statistical analyses, we used the STATA statistical software package, version 15 (StataCorp LP, College Station, TX, USA).

The survey was approved by the Research Ethics Committee of the Federal University of Santa Catarina (Ruling nos. 306/2005 and 009/2007).The SESI, which was a partner in the survey, authorized this secondary data analysis.

RESULTS

The sample consisted of 47,328 workers, of whom 33,057 (69.2%) were male. The prevalence of smoking among the workers was 13.0% (15.2% in men and 7.9% in women; Table 1).

Among men, the smoking prevalence rates were highest in those who were < 30 years of age (38.6%), those who were married (61.8%), those who had completed high school (37.0%), those who had a monthly gross family income, in Brazilian reals (R$) of R$601-1,500 (39.7%), those who lived in the northern region of the country (32.5%), those who consumed 1-7 alcoholic drinks per week (47.6%), and those who reported being rarely or only sometimes stressed (84.3%).

In the adjusted analysis (Table 2), age, marital status, level of education, family income, geographic region, weekly alcohol consumption, and stress levels remained associated with smoking.

Among women, the smoking prevalence rates were highest in those who were < 30 years of age (34.2%), those whose marital status was other than married (58.7%), those who had completed high school (45.3%), those who had a monthly gross family income ≤ R$600 (37.0%), those who lived in the northeastern region of the country (24.7%), those who did not drink alcohol (54.9%), and those who reported being rarely or only sometimes stressed (74.4%). In the adjusted analysis

Chart 1. Study variables.

Variable	Response options	Operational categories
Dependent		
Smoking	I have never smoked[2] I quit over 2 years ago[2] I quit less than 2 years ago[2] I smoke < 10 cigarettes/day[1] I smoke 10-20 cigarettes/day[1] I smoke > 20 cigarettes/day[1]	Smokes[1] Does not smoke[2]
Independent		
RD	Any of the 24 RDs participating in the survey, grouped by geographic region	Southeast South Central-West Northeast North
Gender	Male Female	Male Female
Age	< 30 years 30-39 years 40-49 years ≥ 50 years	< 30 years 30-39 years ≥ 40 years
Marital status	Single[2] Married/Living with a partner[1] Widowed[2] Divorced/Separated[2]	Married[1] Other[2]
Level of education	< 9 years of schooling 9 years of schooling High school graduate College graduate	< 9 years of schooling 9 years of schooling High school graduate College graduate
Gross family income[a]	≤ R$600 R$601-1,500 R$1,501-3,000 > R$3,000	≤ R$600 R$601-1,500 > R$1,500
Alcohol consumption[b]	0 drinks 1-7 drinks 8-14 drinks ≥ 15 drinks	Does not drink 1-7 drinks ≥ 8 drinks
Stress levels[c]	Rarely stressed Sometimes stressed Almost always stressed Always stressed	Rarely/sometimes stressed Almost always/always stressed

RD: regional department; and R$: Brazilian reals. [a]The national monthly minimum wage was R$350 in 2006, R$380 in 2007, and R$415 in 2008. [b]Number of alcoholic drinks consumed per week. [c]Perceived stress levels over time.

(Table 3), the following variables remained associated with smoking: age group (30-39 years and ≥ 40 years); marital status (married); level of education (high school graduate and college graduate); geographic region (northeastern and northern); weekly alcohol consumption (1-7 drinks and ≥ 8 drinks); and stress level (almost always/always stressed).

DISCUSSION

In the present study, 1 in every 10 female industrial workers and 2 in every 10 male industrial workers smoked. The association analyses indicated that being > 30 years of age, consuming alcohol, and having a high stress level were associated with a higher prevalence of smoking in men and women, whereas living in the South or North was associated with a higher prevalence of smoking only in men. In contrast, having a higher level of education and being married were associated with a lower prevalence of smoking, regardless of gender. Having an intermediate family income (R$601-1,500) and living in the northeastern region of the country were associated with a lower prevalence of smoking in men, whereas living in the northeastern or northern region was associated with a lower prevalence of smoking in women.

Between 1990 and 2015, the prevalence of smoking declined considerably in the Brazilian population, and that decline can be attributed to control, regulation, and prevention policies.[3,11] As an example, we highlight the National Program for Smoking Control, which has the objective of reducing the prevalence of smoking through a model in which educational, communication, and health care interventions, as well as legislative and economic measures, work in concert to prevent smoking initiation, promote smoking cessation, and

Table 1. Smoking prevalence, by demographic and socioeconomic variables, alcohol consumption, and stress levels, among industrial workers (N = 47,328). Brazil, 2006-2008.

Variable	Sample size, n	Smoking		
		n	Total, %[a]	Smoking, %[b]
Smoking	47,328	6,163	13.02	100.0
Gender	47,328			
Women		1,126	7.89	18.27
Men		5,037	15.24	81.73
Age, years	47,142			
< 30		2,317	10.66	37.79
30-39		1,921	13.16	31.33
≥ 40		1,893	17.53	30.88
Marital status	47,211			
Other		2,577	12.49	41.96
Married		3,564	13.41	58.04
Level of education	47,230			
< 9 years of schooling		1,963	21.98	31.92
9 years of schooling		1,210	16.35	19.68
High school graduate		2,374	9.84	38.61
College graduate		602	8.88	9.79
Gross family income[c]	46,872			
≤ R$600		2,358	15.69	38.66
R$601-1,500		2,380	12.26	39.02
≥ R$1,501		1,362	10.95	22.33
Geographic region	47,328			
Southeast		721	12.03	11.70
South		924	13.03	14.99
Central-West		1,130	13.89	18.34
Northeast		1,555	10.71	25.23
North		1,833	15.80	29.74
Alcohol consumption[d]	47,052			
0 drinks		2,186	8.06	35.65
1-7 drinks		2,826	17.32	46.09
≥ 8 drinks		1,119	31.12	18.25
Stress levels[e]	47,205			
Rarely/sometimes stressed		5,069	12.45	82.48
Almost always/always stressed		1,077	16.57	17.52

R$: Brazilian reals. [a]Smoking prevalence relative to the sample as a whole. [b]Proportion of the total number of smokers. [c]The national monthly minimum wage was R$350 in 2006, R$380 in 2007, and R$415 in 2008. [d]Number of drinks consumed per week. [e]Perceived stress levels over time.

protect the population from exposure to environmental tobacco smoke.[19]

The present study showed that men smoke more than women, corroborating data in the literature, which suggest that this is attributable to the fact that women adopt healthier lifestyles and take better care of their health, consequently making more positive health choices.[20,21]

The relationship between smoking and age found among industrial workers appears to be similar to that reported for the general population.[3,11] Data from a survey conducted in Brazil in 2017[4] indicate that the prevalence of smoking among adults is higher in the 45- to 54-year age group (11.2%) than in the 18- to 24-year age group (8.5%). Although youth is the period of life when most people have their first experiences with cigarettes, young people smoke less in Brazil, a possible reflection of campaigns and interventions aimed at nonsmokers[22] and of intersectoral public policies, such as the School Health Program and the Health Knowledge Program, which address smoking prevention in schools.[23] In addition, Brazilian law acts to reduce access of young people to tobacco, prohibiting the sale of cigarettes to minors, the advertisement of tobacco products in the media, and tobacco industry sponsorship of sporting and cultural events.[19] Furthermore, an industrialized goods tax has been put on cigarettes, which has increased the retail price.[24]

Our results show that marital status was associated with smoking, indicating that being married/living with a partner is a protective factor against smoking. Several explanations for this emerge from the assumption that marital relationships appear to produce a series of results

Table 2. Smoking prevalence and smoking prevalence ratios, by demographic and socioeconomic variables, alcohol consumption, and stress levels, among male industrial workers (N = 5,037). Brazil, 2006-2008.

Variable	Sample size, n	n (%)	Crude PR (95% CI)	p	Adjusted PR (95% CI)	p
Age, years	5,011			< 0.001		< 0.001
< 30		1,934 (38.6)	1.00		1.00	
30-39		1,540 (30.8)	1.18 (1.10-1.26)		1.22 (1.14-1.31)	
≥ 40		1,537 (30.6)	1.49 (1.40-1.60)		1.55 (1.45-1.67)	
Marital status	5,015			0.168		0.002
Other		1,916 (38.2)	1.00		1.00	
Married		3,099 (61.8)	1.04 (0.98-1.10)		0.91 (0.85-0.97)	
Level of education[a]	5,023			< 0.001		< 0.001
< 9 years of schooling		1,719 (34.3)	1.00		1.00	
9 years of schooling		1,026 (20.4)	0.76 (0.71-0.83)		0.80 (0.74-0.87)	
High school graduate		1,864 (37.0)	0.48 (0.45-0.51)		0.51 (0.48-0.55)	
College graduate		414 (8.3)	0.46 (0.42-0.52)		0.47 (0.41-0.53)	
Gross family income[a,b]	4,990			< 0.001		0.228
≤ R$600		1,947 (39.0)	1.00		1.00	
R$601-1,500		1,982 (39.7)	0.80 (0.75-0.85)		0.91 (0.85-0.97)	
≥ R$1,501		1,061 (21.3)	0.72 (0.67-0.77)		0.96 (0.88-1.05)	
Geographic region[c]	5,037			< 0.001		0.015
Southeast		546 (10.8)	1.00		1.00	
South		658 (13.1)	1.15 (1.03-1.29)		1.16 (1.03-1.30)	
Central-West		916 (18.2)	1.16 (1.05-1.30)		1.04 (0.93-1.16)	
Northeast		1,278 (25.4)	0.92 (0.83-1.02)		0.84 (0.76-0.93)	
North		1,639 (32.5)	1.40 (1.27-1.54)		1.26 (1.14-1.39)	
Alcohol consumption[d,e]	5,013			< 0.001		< 0.001
0 drinks		1,537 (31.4)	1.00		1.00	
1-7 drinks		2,387 (47.6)	1.90 (1.78-2.02)		1.94 (1.82-2.07)	
≥ 8 drinks		1,053 (21.0)	3.26 (3.01-3.52)		3.24 (2.99-3.51)	
Stress levels[e,f]	5,022			< 0.001		< 0.001
Rarely/sometimes stressed		4,233 (84.3)	1.00		1.00	
Almost always/always stressed		789 (15.7)	1.36 (1.26-1.46)		1.29 (1.19-1.39)	

PR: prevalence ratio; and R$: Brazilian reals. [a]Adjusted for age and marital status. [b]The national monthly minimum wage was R$350 in 2006, R$380 in 2007, and R$415 in 2008. [c]Adjusted for age, marital status, level of education, and gross family income. [d]Weekly. [e]Adjusted for age, marital status, level of education, gross family income, and geographic region. [f]Perceived stress levels over time.

due to the acquisition of different health behaviors, the greater social support received by married subjects apparently promoting smoking cessation, whereas subjects who do not have a partner are more prone to loneliness, have less social support, and experience high levels of stress due to a break-up, all of which may stimulate smoking.[25]

In the present study, the prevalence of smoking was inversely proportional to the level of education, in both genders. This result corroborates the findings of a previous study profiling the Brazilian population, in which the proportion of smokers was shown to be lower among individuals, of either gender, with a higher level of education.[4] In studies conducted in other countries, such as Russia[26] and India,[27] a similar relationship has been observed between educational variables and smoking. In this regard, we emphasize the importance of understanding the factors that influence the adoption of healthy lifestyles and the extent to which the various smoking control interventions reach men and women in different social strata and with different levels of education.[28]

In our study, none of the family income categories were associated with smoking in either gender. Regardless, the impact that spending has on overall family income appears to differ across income brackets, given that higher-income individuals spend proportionately less on tobacco products, while having greater access to resources for smoking cessation.[29]

When analyzing smoking among industrial workers in Brazil by geographic region, we found that, for both genders, workers in the northeastern region were at a lower risk of smoking than were those in the southeastern region. In addition, among women, those in the northern region of the country were at a lower risk of smoking than were those in the southeastern region. A study of adults in Brazil found that the prevalence of daily smoking ranged from 12.8% in the northern region to 17.4% in the southern region.[30] This finding may explain to some extent the higher

Table 3. Smoking prevalence and smoking prevalence ratios, by demographic and socioeconomic variables, alcohol consumption, and stress level, among female industrial workers (N = 1,126). Brazil, 2006-2008.

Variable	Sample size, n	n (%)	Gross PR (95% CI)	p	Adjusted PR (95% CI)	p
Age, years	1,120			< 0.001		< 0.001
< 30		383 (34.2)	1.00		1.00	
30-39		381 (34.0)	1.49 (1.30-1.72)		1.61 (1.39-1.86)	
≥ 40		356 (31.8)	2.22 (1.92-2.57)		2.36 (2.04-2.74)	
Marital status	1,126			0.003		< 0.001
Other		661 (58.7)	1.00		1.00	
Married		465 (41.3)	0.83 (0.74-0.94)		0.73 (0.65-0.83)	
Level of education[a]	1,126			< 0.001		< 0.001
< 9 years of schooling		244 (21.6)	1.00		1.00	
9 years of schooling		184 (16.3)	0.72 (0.60-0.88)		0.83 (0.68-1.01)	
High school graduate		510 (45.3)	0.45 (0.39-0.53)		0.54 (0.46-0.65)	
College graduate		188 (16.8)	0.43 (0.36-0.52)		0.47 (0.38-0.60)	
Cross family income[a,b]	1,110			< 0.001		0.665
≤ R$600		411 (37.0)	1.00		1.00	
R$601-1,500		398 (35.9)	0.73 (0.64-0.84)		0.87 (0.75-1.00)	
≥ R$1,501		301 (27.1)	0.73 (0.63-0.85)		0.97 (0.81-1.16)	
Geographic region[c]	1,126			< 0.001		< 0.001
Southeast		175 (15.5)	1.00		1.00	
South		266 (23.6)	1.04 (0.86-1.25)		0.98 (0.80-1.19)	
Central-West		214 (19.0)	1.02 (0.84-1.25)		0.92 (0.75-1.13)	
Northeast		277 (24.7)	0.73 (0.61-0.88)		0.64 (0.53-0.77)	
North		194 (17.2)	0.74 (0.61-0.91)		0.72 (0.58-0.88)	
Alcohol consumption[d,e]	1,118			< 0.001		< 0.001
0 drinks		613 (54.9)	1.00		1.00	
1-7 drinks		439 (39.1)	2.38 (2.11-2.70)		2.52 (2.23-2.86)	
≥ 8 drinks		66 (6.0)	5.05 (3.92-6.51)		5.04 (3.89-6.54)	
Stress levels[e,f]	1,124			< 0.001		< 0.001
Rarely/sometimes stressed		836 (74.4)	1.00		1.00	
Almost always/always stressed		288 (25.6)	1.61 (1.40-1.84)		1.49 (1.30-1.70)	

PR: prevalence ratio; and R$: Brazilian reals. [a]Adjusted for age and marital status. [b]The national monthly minimum wage was R$350 in 2006, R$380 in 2007, and R$415 in 2008. [c]Adjusted for age, marital status, level of education, and gross family income. [d]Weekly. [e]Adjusted for age, marital status, level of education, gross family income, and geographic region. [f]Perceived stress levels over time.

prevalence of smoking in the southern region, because two of the three states in this region, Rio Grande do Sul and Santa Catarina, are responsible for most of the national production of tobacco, which may be leading to higher tobacco use in this region.[31] In addition, the higher tobacco use in this region may be attributed to cultural factors, such as the strong influence of its European immigrants and its proximity to countries such as Argentina and Uruguay, where the prevalence of smoking is close to 30%.[11] Likewise, some prevalence studies coordinated by the Brazilian federal government also report that the number of smokers is higher in the southern region.[15,31-33]

With regard to alcohol consumption, we found that an increase in the number of drinks consumed per week was paralleled by an increase in the prevalence of smoking. This finding is similar to those reported in other studies in Brazil, which assessed associations in risk behaviors in adults.[8,34] A study that monitored the prevalence of health-related characteristics and behaviors in the United States, Guam, Puerto Rico, and the Virgin Islands found that smokers are more likely to drink compulsively than are former smokers or nonsmokers.[35] Therefore, the co-use of alcohol and nicotine leads to a greater desire to consume both substances.[36] The nature of the relationship between nicotine and alcohol suggests that the severity of dependence on these drugs should be considered jointly.[37] According to the World Health Organization, there is a growing worldwide trend toward people using various psychoactive substances together and at different times, leading to increased health risks.[38]

The findings of the present study showed that the prevalence of smoking was higher among workers with higher stress levels, for both genders. This bidirectional relationship can occur, as reported in a study of occupational stress among bank workers that found that smoking was significantly associated with stress.[39] It is plausible that this relationship is due to occupational pressure resulting from the precariousness of employment, an accumulation of

duties, and increased responsibility, all of which imply susceptibility to stress,[40] reinforcing tobacco use.[7]

Our study has some limitations. First, the results are dependent on the criterion used to define "smoking", and comparisons should consider this aspect. Second, the data are representative of industrial workers in Brazilian capitals and may not reflect the reality of workers in other locations or other work settings. Third, the data are representative of a 2006-2008 scenario and may not portray the current situation. Finally, the sample specifically included adult workers, therefore not being representative of the elderly population.

The current debate on occupational health should consider the ongoing changes in the world of labor, so that the lifestyle of workers can be improved. Our results showed that the behavior of variables such as gender, age, level of education, alcohol consumption, and stress levels among industrial workers is similar to that found in the general population, indicating that the understanding may be similar. Nevertheless, further studies, such as longitudinal surveys that allow monitoring of the real impact of these and other variables on smoking in this population and intervention studies that allow testing of interventions for behavior change, should be encouraged.

In summary, our study revealed that 1 in every 10 industrial workers smokes, the prevalence of smoking being higher in men and in workers > 30 years of age.

In addition, alcohol consumption and high stress levels are factors that potentiate smoking.

AUTHOR CONTRIBUTIONS

PMS and KSS participated in the study design, assisted in the literature review and in the interpretation of data, participated in the writing and critical review of the manuscript, and approved the final version. GTM and MTGK participated in the study design, assisted in the analysis and interpretation of data, participated in the writing and critical review of the manuscript, and approved the final version. AFB and MVN prepared and coordinated the project, collected the data, participated in the writing and critical review of the manuscript, and approved the final version.

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2020 Brazilian Thoracic Association recommendations for the management of asthma

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ABSTRACT

The pharmacological management of asthma has changed considerably in recent decades, as it has come to be understood that it is a complex, heterogeneous disease with different phenotypes and endotypes. It is now clear that the goal of asthma treatment should be to achieve and maintain control of the disease, as well as to minimize the risks (of exacerbations, disease instability, accelerated loss of lung function, and adverse treatment effects). That requires an approach that is personalized in terms of the pharmacological treatment, patient education, written action plan, training in correct inhaler use, and review of the inhaler technique at each office visit. A panel of 22 pulmonologists was invited to perform a critical review of recent evidence of pharmacological treatment of asthma and to prepare this set of recommendations, a treatment guide tailored to use in Brazil. The topics or questions related to the most significant changes in concepts, and consequently in the management of asthma in clinical practice, were chosen by a panel of experts. To formulate these recommendations, we asked each expert to perform a critical review of a topic or to respond to a question, on the basis of evidence in the literature. In a second phase, three experts discussed and structured all texts submitted by the others. That was followed by a third phase, in which all of the experts reviewed and discussed each recommendation. These recommendations, which are intended for physicians involved in the treatment of asthma, apply to asthma patients of all ages.

Keywords: Asthma/therapy; Asthma/drug therapy; Asthma/prevention & control; Practice guideline.

INTRODUCTION

The pharmacological management of asthma has changed considerably in recent decades, based on the understanding that asthma is a complex and heterogeneous disease, with different phenotypes and endotypes. This knowledge has changed the strategies for managing the disease, making way for the emergence of new drugs to control asthma. Several recent international guidelines and recommendations summarize the criteria for the treatment of asthma in steps, allowing an overall view of the incremental increases in the control treatment as the severity of asthma increases.[1-6] Despite these advances, the level of control of the disease remains low, with high morbidity, irrespective of the country studied.[7,8]

The heterogeneity of asthma is evidenced by the various phenotypes (observable characteristics of an individual) and endotypes (molecular or pathophysiological mechanism underlying the phenotype) of the disease. Among the more frequently used inflammatory phenotypes are eosinophilic asthma, noneosinophilic asthma,

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allergic asthma, and nonallergic asthma. The various endotypes include high and low Th2-driven inflammation, designated the Th2-high and Th2-low subtypes, respectively.[9] Asthma patients with the Th2-high subtype usually present early-onset asthma that is more severe, accompanied by atopy/IgE and airway and systemic eosinophilia. Asthma patients with the Th2-high subtype tend to be responsive to corticosteroids and drugs that inhibit Th2-driven inflammation.[10] In contrast, those with the Th2-low subtype generally have late-onset asthma, with no airway or systemic eosinophilia, and show reduced responsiveness to corticosteroids. Patients with the Th2-low subtype also do not respond to the drugs that inhibit Th2-driven inflammation.[9]

Evidence from studies of induced sputum samples show that the majority of asthma patients have a concordant type of disease; that is, as the airway inflammation increases, the symptoms increase, and as the airway inflammation decreases the symptoms decrease.[11] Therefore, for the great majority of asthma patients, the treatment may be guided by the symptoms, the dose of anti-inflammatory medication being increased or decreased to achieve and maintain control of the disease.

The present recommendations apply to adults and children with asthma. They are intended for clinicians involved in the treatment of asthma in clinical practice, except for severe asthma, which will be discussed in greater depth in another set of recommendations. With the objective of critically summarizing recent evidence of the pharmacological treatment of asthma, we brought together 22 experts from Brazil to draw up the present recommendations, a guide for asthma treatment adapted for use in Brazil. The themes were selected by the panel of experts, who chose topics or questions relating to the most significant changes in the concepts and, consequently, in the management of asthma in clinical practice. Each expert was invited to provide a critical review of a topic or to respond to a question from those recommendations. In a second phase, three experts discussed and structured all of the texts received from the others. In a third phase, all of the experts reviewed and discussed the present recommendations.

Concept

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheezing, dyspnea, retrosternal chest pressure, and cough, all of which vary longitudinally and in intensity, accompanied by variable airflow limitation.[1]

Epidemiology of asthma in Brazil

The prevalence of asthma symptoms among adolescents in Brazil, according to international studies, was 20%—one of the highest in the world—in 2007.[12] A study by the World Health Organization indicated that, among adults 18-45 years of age in Brazil, 23% had experienced symptoms of asthma within the previous year,[13] although only 12% had previously been diagnosed with asthma. A study conducted in 2012, involving 109,104 adolescents, also found that 23% had asthma symptoms and 12% had previously been diagnosed with asthma.[14]

In 2013, there were 129,728 hospitalizations and 2,047 deaths due to asthma in Brazil. The rates of asthma-related hospitalization and mortality are decreasing in most regions, in parallel with increased access to treatment.[15] Uncontrolled asthma generates high costs for the health care system as well as for families.[16] In cases of severe asthma, it is estimated that this corresponds to more than a quarter of the family income among users of the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System),[16,17] although the cost could be reduced significantly with the adequate control of the disease.[18] However, a nationwide survey found that only 12.3% of asthma patients had well-controlled asthma.[19]

Various interventions at the municipal level have been shown to be effective in controlling asthma symptoms, as well as in reducing the number of exacerbations and hospitalizations.[20,21] However, the problems with underdiagnosis and lack of training among primary health care professionals[22] require action. A nationwide experiment in training Family Health Program teams in the treatment of chronic respiratory diseases through collaborative care, with the support of experts, has been successful and could be expanded.[23]

Difference between asthma control and severity

The concept of asthma control comprises two distinct domains[1,24]: the control of current clinical limitations, such as minimal symptoms during the day, the absence of symptoms at night, a reduced need for rescue medication, and no limitation of physical activities; and the reduction of future risks, such as exacerbations, accelerated loss of lung function, and adverse treatment effects. On the basis of those parameters, asthma can be classified as controlled, partially controlled, or uncontrolled (Chart 1).[1,25,26] The degree of control is typically evaluated by considering the last 4 weeks.

Asthma education and the judicious management of medication therapy are key to controlling the disease. The periodic assessment of asthma control is an important dynamic marker of the severity of the disease and the main parameter for determining the need to adjust the treatment plan.

Currently, in addition to the asthma control questionnaire created by the Global Initiative for Asthma (GINA),[1] other tools have been culturally adapted for use in Brazil, including the Asthma Control Questionnaire[25] and the Asthma Control Test.[26] The advantage of using these last two tools is their numerical evaluation (Chart 1), which facilitates understanding of the level of asthma control by the patient and the physician. Although spirometry is not part of either

Chart 1. Definition of asthma control by different instruments.

Instrument/items	Controlled asthma	Partially controlled asthma	Uncontrolled asthma
GINA[1]			
Diurnal symptoms > 2 times per week	None	1-2 items	3-4 items
Nocturnal awakenings due to asthma			
Rescue medication > 2 times per week			
Limitation of activities due to asthma			
ACQ-7[25] [a]		**Score**	
Number of nocturnal awakenings	≤ 0.75	0.75 to < 1.5	> 1.5
Intensity of symptoms			
Limitation of activities due to asthma			
Intensity of dyspnea			
Wheezing (how long)			
Rescue medication			
Pre-bronchodilator FEV_1			
ACT[26]		**Score**	
Limitation of activities due to asthma	≥ 20	15-19	≤ 15
Dyspnea			
Nocturnal awakenings due to asthma			
Rescue medication			
Self-assessment of asthma control			

GINA: Global Initiative for Asthma; ACQ-7: 7-item Asthma Control Questionnaire – 0-7 points per item; ACT: Asthma Control Test – 0-5 points per item. [a]The ACQ can be used without spirometry; in this case, it is referred to as ACQ-6. If used without spirometry or rescue medication, it is referred to as ACQ-5.

the GINA questionnaire for the evaluation of asthma control[1] or the Asthma Control Test,[26] it should be performed, if available, every 3-6 months in order to estimate the future risk of exacerbations and accelerated loss of lung function.

Although the concept of asthma control expresses the degree with which the manifestations of asthma are suppressed by treatment, varying over periods of days or weeks, the concept of asthma severity refers to the quantity of medication needed to attain control, reflecting a characteristic of the disease that can change slowly over time.[1]

Factors that influence asthma control

The factors that influence the response to asthma treatment include the following: misdiagnosis; lack of adherence; use of medications that can decrease the response to treatment (nonsteroidal anti-inflammatory drugs and beta-blockers); indoor exposure (e.g., to dust or smoke); occupational exposure; smoking; and other comorbidities. Therefore, it is recommended that the factors that influence asthma control be checked prior to any modification in the treatment of patients with asthma, partially controlled or not controlled.[1]

Adherence to treatment

The main cause of poor asthma control is low adherence to treatment due to voluntary factors (fears and myths about the treatment) or involuntary factors (lack of access to treatment or difficulty in using an inhaler).[1] At present, adherence to asthma treatment remains low.[19] Difficulty in detecting nonadherence is the main obstacle to addressing this problem. A nationwide survey revealed that only 32% of the asthma patients in Brazil are compliant with treatment.[19] Although assessments through medical history, counting medications, verifying pharmacy records, detecting side effects, and using other methods at our disposal have not proven sufficient, the must nevertheless be employed. There is growing interest in the development of more accurate methods of measuring adherence to treatment, and the use of electronic devices could be an option.[27,28]

Smoking

Exposure to second-hand smoke, in children and adults, increases the risk of exacerbations and impairs asthma control. In addition, smoking increases the severity of asthma, hampers its control, accelerates the loss of lung function, and decreases the responsiveness to inhaled corticosteroids (ICS).[1,29] Smokers with asthma have an increased risk of hospitalization and severe exacerbation.

Environmental and occupational exposure

Environmental exposure (e.g., to dust and pollutants), whether at home (from biomass burning, mites, cockroach allergens, animal dander, etc.) or at work (from latex, low-molecular-weight agents, and cleaning materials) are important factors associated with the difficulty of asthma control. In addition, occupational exposure may be the cause of asthma (occupational asthma).[30]

That is why it is important to investigate each patient in relation to their associated exposures and, when identified, these should be eliminated or minimized,

if possible (especially for patients with occupational asthma).

Use of other drugs that may impair asthma control

Aspirin and other nonsteroidal anti-inflammatory drugs can cause severe asthma exacerbation in sensitized individuals, and beta-blockers (in oral or ophthalmic formulations) may cause bronchospasm. Therefore, the decision about their use should be considered individually, weighing the risks and benefits.[1]

Comorbidities

A thorough investigation of all of the factors associated with difficult-to-control asthma in every asthma patient is unnecessary.[31] However, in cases of difficult-to-control asthma, which affects 17.4% of all adult asthma patients and 74.1% of those in treatment classified as GINA step 4 or 5,[32] a systematic investigation must be performed to identify, minimize, or eliminate comorbidities (such as gastroesophageal reflux, obesity, vocal cord dysfunction, chronic rhinosinusitis, nasal polyposis, anxiety, depression, sleep apnea, COPD, allergic bronchopulmonary aspergillosis, and bronchiectasis) and to avoid asthma being caused or worsened by occupational exposure, among other things that can impair the disease control.

THE PREFERRED TREATMENT FOR ASTHMA CONTROL

The treatment of asthma seeks to achieve or maintain the current level of control of the disease and to prevent future risks (exacerbations, instability of the disease, accelerated loss of lung function, and adverse effects of treatment).[1] In addition to pharmacological treatment, this requires a personalized approach including patient education, a written action plan, training in the use of the inhaler, and reviewing the inhalation technique at each visit.

The basis of pharmacological treatment for asthma is the use of an ICS, with or without a long-acting β_2 agonist (LABA). These medications are available for use in Brazil in a variety of dosages and inhaler devices (Table 1). In clinical practice, choosing the medication, the inhaler, and its dosage should be based on the assessment of symptom control, patient characteristics (risk factors, ability to use the inhaler in a correct manner, and cost), the preference of the patient for the inhaler device, clinical judgment, and the availability of the medication. Therefore, there is no single medication, dose, or inhaler that applies without distinction to all patients with asthma.

In the GINA, asthma control treatment is divided into steps 1 through 5[1], in which the dose of ICS is progressively increased or other controller medications are added (Figures 1-3). The recommended controller medications at the different treatment steps are described below.

ICS

The efficacy of the different types of ICS varies depending on their pharmacokinetics and pharmacodynamics, as well as on pulmonary deposition and adherence to treatment.[1,33,34] The equivalence of the different types of ICS, divided into low, medium, and high dosages, is described in Table 2.[1,3,5,6,24] The assessment of the response to treatment with ICS should be made through the combination of clinical and functional parameters. After obtaining and maintaining asthma control for an extended time (not less than 3 months), the ICS dose can be reduced to a minimum, with the aim of using the lowest possible dose to maintain asthma control.

The use of an ICS can cause local adverse effects, such as throat irritation, dysphonia, and candidiasis.[1,35] The use of a pressurized, metered-dose inhaler with a spacer decreases the risk of adverse effects, as does oral hygiene after inhalation of each dose of ICS. The use of high doses of ICS for prolonged periods increases the risk of systemic adverse effects, such as reduction of bone mineral density, respiratory infections (including tuberculosis), cataracts, glaucoma, and suppression of the hypothalamic-pituitary-adrenal axis.[1,36-39]

ICS-LABA combination

Combining an ICS with a LABA or an ultra-LABA is the preferred control treatment in GINA steps 3 and 4[1]; that is, when treatment with ICS alone is not sufficient to achieve and maintain control of the disease. The evidence for using the ICS-LABA combination as the preferred control therapy in GINA steps 3-5 is robust.[40-47]

In its most recent edition, the GINA expanded upon that recommendation, suggesting the combination of low dose ICS and as-needed formoterol as the preferred asthma control treatment in step 1. In GINA step 2, two options are given[1]: continuous low dose ICS therapy or an ICS+as-needed formoterol.

In GINA step 1, the recommendation for the use of ICS+formoterol for asthma patients > 12 years of age is based on indirect evidence from other studies employing that combination in patients with mild asthma.[48] The current GINA[1] recommendations for step 2 treatment are based on two large, controlled, double-blind randomized clinical trials (RCTs) of non-inferiority that assessed the use of as-needed low-dose budesonide+formoterol (200 µg and 6 µg, respectively) versus fixed-dose ICS, for a period of 52 weeks, in patients with mild asthma.[49,50] The results show that a fixed-dose ICS was better in the control of symptoms; however, for the reduction of exacerbations, the as-needed budesonide+formoterol option was not inferior and was superior to the use of a short-acting β_2 agonist (SABA) alone. More recently, these results were confirmed in a pragmatic, open-label study.[51]

The rationale for using ICS+LABA is based on strong evidence that this combination is more effective in controlling the symptoms of asthma, reducing

Table 1. Inhaled asthma controller medications available in Brazil.[a]

Inhaled corticosteroid alone				
Medications	Inhaler (number of doses)	Trade name®	Dose administered	Age approved in the insert
BDP (HFA)[b]	pMDI (200)	Clenil spray	50 µg	Children and adults
			200 or 250 µg	Only adults
BDP	DPI capsules (60)	Miflasona	200 or 400 µg	Children and adults
BUD	DPI capsules (15 and 60)	Busonide caps	200 or 400 µg	≥ 6 years
	Aerolizer (30 and 60)	Miflonide		
FTC	Diskus (60)	Flixotide	50 or 250 µg	≥ 4 years
FTC (HFA)	pMDI (60 or 120)	Flixotide spray	50 µg	≥ 1 year
			250 µg	≥ 4 years
MOM	DPI - Capsules (60)	Oximax	200 or 400 µg	≥ 12 years
Inhaled corticosteroids in combination with LABA				
Medications	Inhaler (number of doses)	Trade name®	Dose administered	Age approved in the insert
FORM + BUD -	Aerocaps single capsule (15/30/60)	Alenia	6/100 µg or 6/200 µg	≥ 4 years
			12/400 µg	≥ 6 years
FORM + BUD -	Aerolizer separate capsules (60)	Foraseq	6/100 µg or 6/200 µg	≥ 12 years
FORM + BUD -	Turbuhaler (60)	Symbicort Turbuhaler	6/100 µg or 6/200 µg	≥ 4 years
			12/400 µg	≥ 12 years
FORM + BUD (HFA) -	pMDI (120)	Symbicort; Vannair spray	6/100 µg	≥ 6 years
			6/200 µg	≥ 12 years
FORM + BDP (HFA)[b]	pMDI (120)	Fostair spray	6/100 µg	≥ 18 years
FORM + BDP[b]	Next (120)	Fostair DPI	6/100 µg	≥ 18 years
FORM + FP	CDM-Haller single capsule (60)	Lugano	12/250 µg	≥ 12 years
SALM + FP (HFA)	Diskus (60)	Seretide Diskus	50/100 µg	≥ 4 years
			50/200 µg or 50/500 µg	≥ 12 years
SALM + FP (HFA)	pMDI (120)	Seretide spray	25/50 µg	≥ 4 years
			25/125 µg or 25/250 µg	≥ 12 years
Inhaled corticosteroid in combination with a SABA				
Medications	Inhaler (number of doses)	Trade name®	Dose administered	Age approved in the insert
BDP (HFA)	pMDI (200)	Clenil Compositum HFA	50/100 µg	≥ 6 years
	Solution for nebulization	Clenil Compositum A	400 µg g/mL and 800 µg/mL	Children and adults
Inhaled corticosteroid in combination with an ultra-LABA				
Medications	Inhaler (number of doses)	Trade name®	Dose administered	Age approved in the insert
FF + VI	Ellipta (30)	Relvar	100/25 µg or 200/25 µg	≥ 12 years
LAMA				
Medications	Inhaler (number of doses)	Trade name®	Dose administered	Age approved in the insert
Tiotropium (AC)	Respimat (60)	Spiriva	2.5 µg	≥ 6 years

BDP: beclomethasone dipropionate; HFA: hydrofluoroalkane; pMDI: pressurized metered-dose inhaler; DPI: dry powder inhaler; BUD: budesonide; FP: fluticasone propionate; MOM: mometasone furoate; LABA: long-acting β_2 agonist; FORM: formoterol fumarate; SALM: salmeterol xinafoate; SABA: short-acting β_2 agonist; FF: fluticasone furoate; VI: vilanterol; LAMA: long-acting muscarinic antagonist; and AC: aerosol "cloud". [a]The recommendations for each dose of medication were taken from the package inserts of medications approved by the Brazilian National Health Oversight Agency. The equivalence of medications in this table and ages with evidence for clinical use should be verified. [b]Extra fine particles.

exacerbations, and slowing the loss of lung function after exacerbations than is an ICS alone.[40-47,52] In addition, there is evidence showing that the ICS-LABA combination has a synergistic effect, which allows more anti-inflammatory efficacy with a smaller dose of ICS and, consequently, fewer adverse effects.[53]

Two recent studies involving a large number of adults and adolescents with asthma using the ICS-LABA

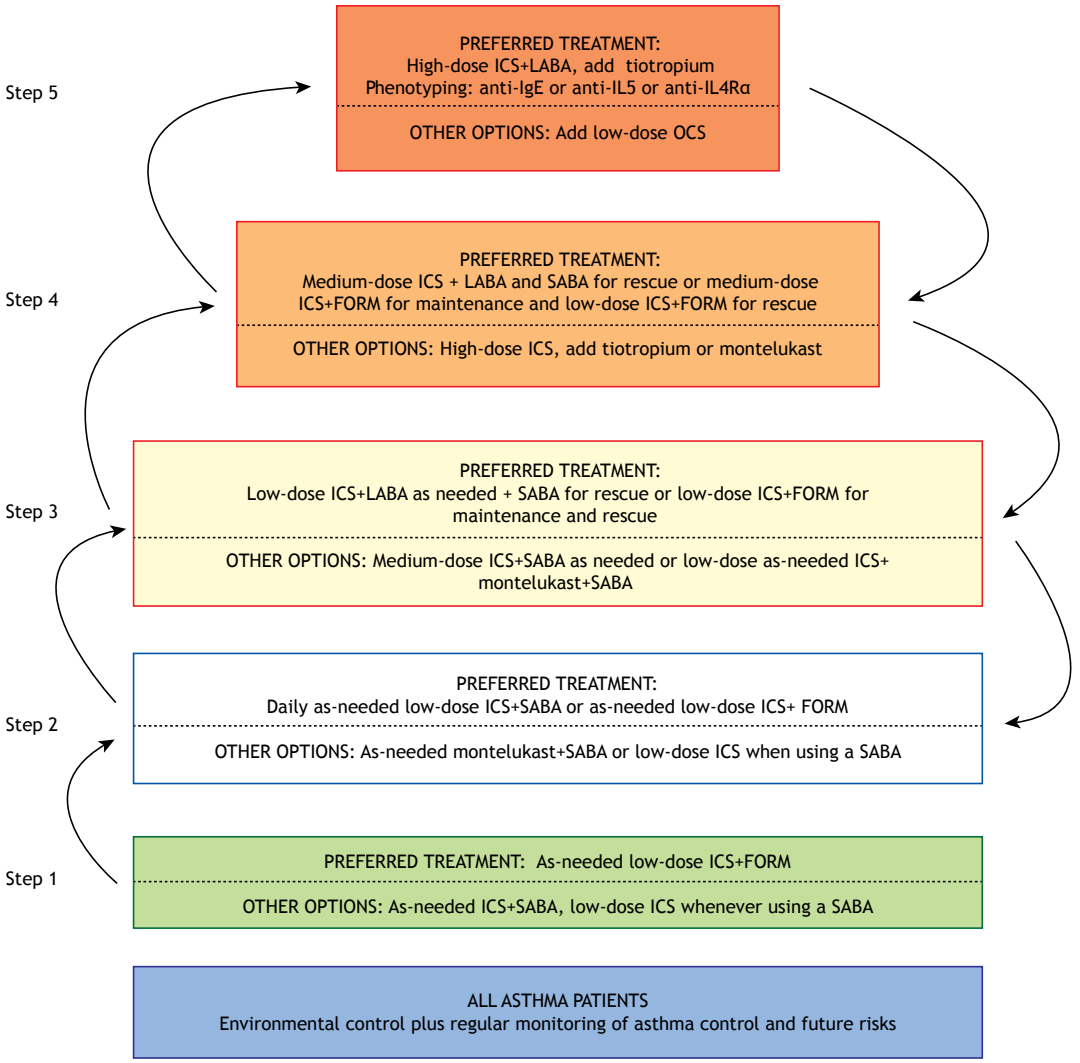

Figure 1. Asthma management for patients ≥ 12 years of age. ICS: inhaled corticosteroid(s); LABA: long-acting β_2 agonist; OCS: oral corticosteroid(s); SABA: short-acting β_2 agonist; and FORM: formoterol fumarate.

combination compared with those using the same dose of ICS alone showed 16.5%[45] and 21.0%[46] fewer severe exacerbations, respectively, in those using the former. This effect was even more pronounced among adolescents, in whom the risk of severe asthma exacerbations was 35% lower when the ICS-LABA combination was used.[45]

The safety of the ICS-LABA combination was tested in multicenter and multinational RCTs in adults[45,46] and children,[47] carried out under the auspices of the US Food and Drug Administration, involving a total of more than 20,000 patients with asthma who were ≥ 12 years of age and more than 6,000 who were 4-11 years of age.[47] Those studies showed that the budesonide-formoterol and salmeterol-fluticasone combinations do not increase the risk of hospitalization for asthma, the number of asthma-related intubations, or the number of asthma-related deaths in comparison with the use of ICS alone. However, the use of LABA alone in asthma is contraindicated because it increases the risk of asthma-related hospitalization and death.[54] These findings are considered class effects.

Strategy for the use of ICS+LABA: fixed dose or variable dose

The use of the ICS-LABA combination in asthma treatment can be recommended in a fixed dose with the addition of a SABA as rescue medication or in a variable dose with budesonide+formoterol or beclomethasone+formoterol as controller and rescue medications in a single inhaler.[1] The efficacy of the fixed or variable strategies has been confirmed by several meta-analyses, RCTs, and real-life studies.[40-46,55]

To date, there have been no meta-analyses proving the superiority of one strategy over another[44,55], and the GINA therefore recommends the ICS-LABA combination without specifying the strategy (fixed or variable) for the treatment of asthma in steps 3-5.[1] One recent meta-analysis[55] evaluated 64 RCTs (with a collective sample of approximately 60,000 patients) and

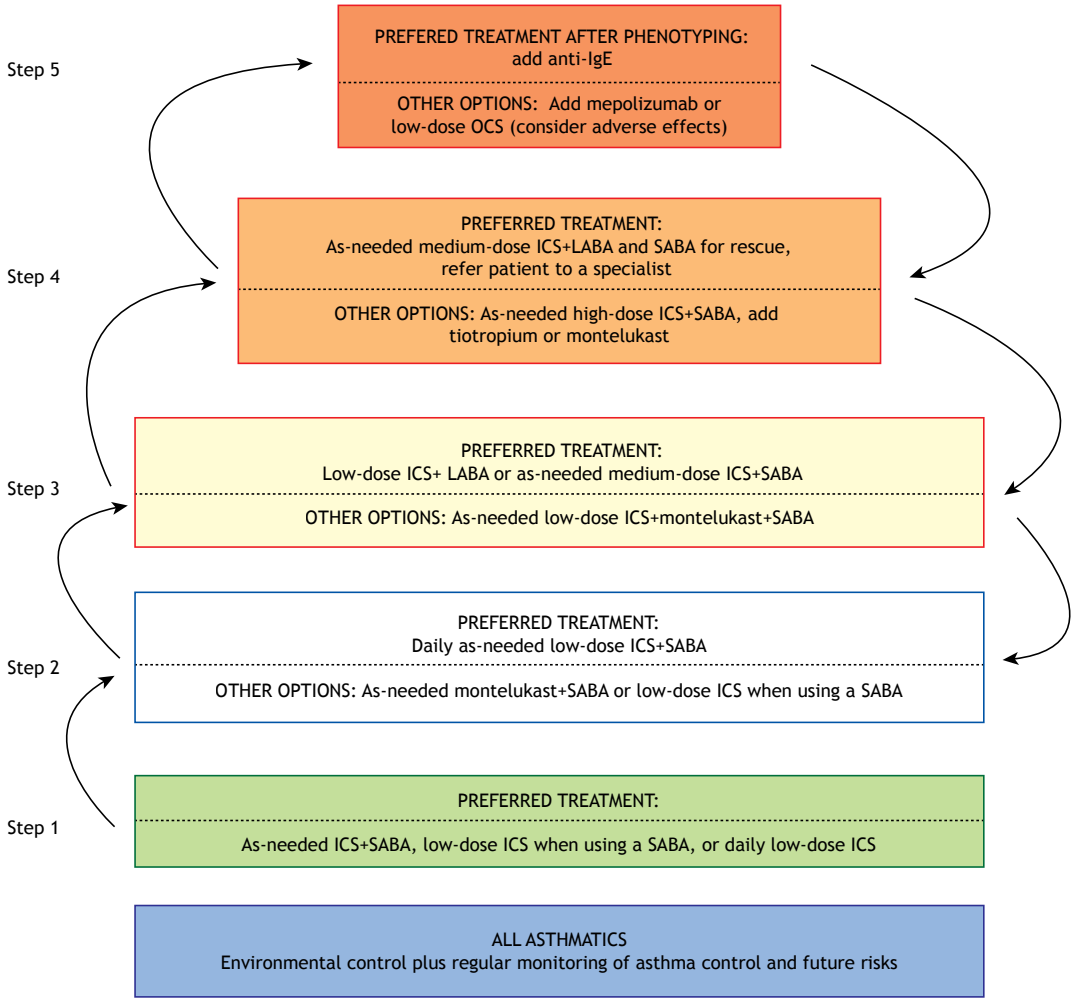

Figure 2. Asthma management in children between 6 and 11 years of age. OCS: oral corticosteroid(s); ICS: inhaled corticosteroid(s); LABA: long-acting β_2 agonist; and SABA: short-acting β_2 agonist.

compared the fixed and variable dose strategies with various ICS-LABA combinations. The results showed that, with either strategy, the use of an ICS-LABA combination is more effective for the prevention of severe asthma exacerbations than is the use of an ICS alone. Therefore, the choice of fixed or variable strategies should be determined by the physician, after the characteristics and preferences of the patient have been evaluated.

In the strategy using ICS+formoterol as controller and rescue medication, the dose is adjusted by the patient when there are symptoms. The rationale is that the anti-inflammatory agent functions as a controller medication and the fast-acting LABA functions as a rescue medication.[41,44,55] It is recommended to use a fixed dose, generally once every 12 h, with additional doses, if necessary, up to six times per day (maximum, 12 inhalations/day). In addition, the controller and rescue medication strategy reduces the risk of exacerbations even with the lower doses of ICS employed.[41,44]

Control-based asthma management in steps

Individualizing the treatment of asthma according to the level of control of the disease, the characteristics/preferences of the patient, and the level of access to treatment[1] requires more frequent consultations (every 3-6 months) and regular monitoring. The rationale for adjusting the asthma treatment is to achieve and maintain control of the disease, as well as to reduce future risks,[1-4,6] with the lowest possible dose of controller medication. Every patient should receive an updated action plan, and the results of the dose adjustment should be monitored, if possible, by objective measures.

The adjustment (increase or decrease) of the dose of controller medication should involve the use of objective tools that indicate the degree of asthma control (Chart 1). If the asthma is not controlled, the medication or dose will be adjusted in accordance with the next step up, whereas it will be adjusted in accordance with the next step down if the asthma is controlled (Figures 1 and 2).

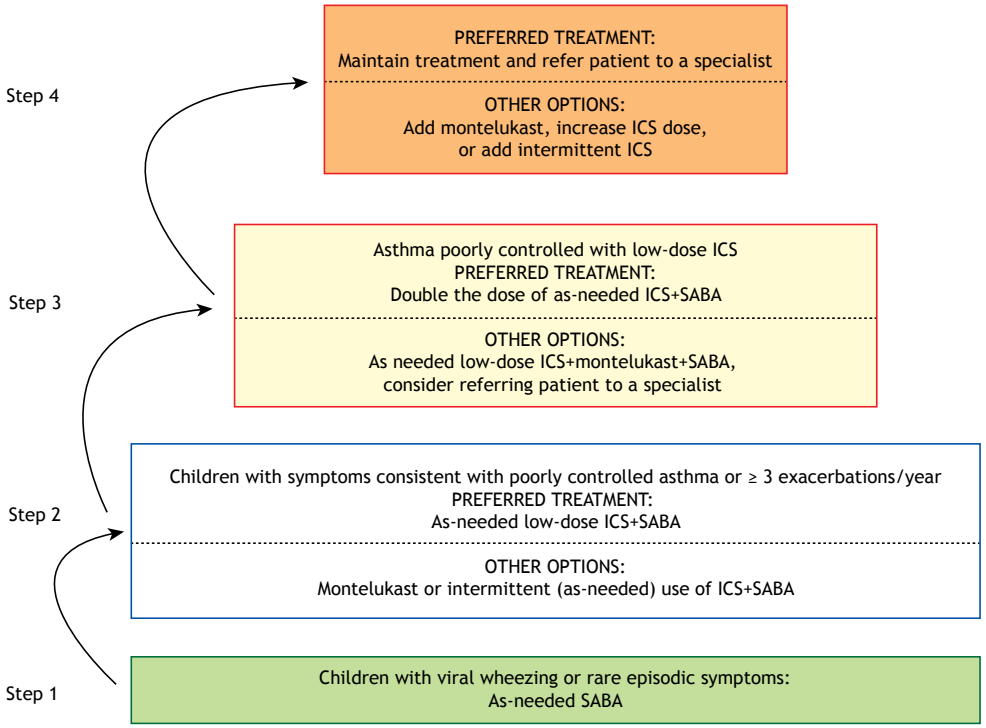

Figure 3. Asthma management for children ≤ 5 years of age. ICS: inhaled corticosteroid(s); and SABA: short-acting β_2 agonist.

Any strategy to increase or decrease the controller medication dose should be patient-centered, including the assessment of asthma stability (defined as current control and the absence of severe exacerbations in the last year), treatment adherence, the control of comorbidities, the risk of exacerbations, occupational/environmental exposure, the treatment level, and the potential adverse effects of medication.[1,56] There have been few studies about the optimal timing of a dose reduction. Reducing the dose too soon increases the risk of exacerbations,[1] as does the cessation of ICS use.[56,57]

In the fixed-dose strategy, the treatment should be adjusted periodically, increasing or decreasing the dose in accordance with the level of control. For patients using ICS+formoterol for control and rescue, the dose is adjusted by the patient in accordance with the self-perception of symptoms, although the control of the disease and functional changes should be monitored.

A recent meta-analysis[58] evaluating six RCTs involving adults with well-controlled asthma receiving ICS alone and three RCTs with the same type of patients receiving ICS+LABA showed that it is possible to reduce the ICS dose by 50-60% without increasing the risk of exacerbations. Although the level of evidence of that study was insufficient to determine whether reducing the ICS dose is more beneficial than harmful, dose reduction should be attempted in order to avoid the use of unnecessarily high doses.

Another possibility for adjusting the controller medication would be to eliminate the LABA from the combination, returning to the use of ICS therapy alone. However, a meta-analysis of studies involving adults[59] showed that the elimination of the LABA leads to a reduction in the quality of life and in asthma control. A subanalysis of a recent RCT[45] comparing the ICS+LABA combination with ICS alone showed that, in patients with asthma that was well controlled with ICS+LABA, the shift to ICS alone significantly increased the risk of exacerbations. Therefore, the withdrawal of the LABA is not recommended for patients in whom asthma is controlled with ICS+LABA.

ALTERNATIVES FOR ASTHMA CONTROL TREATMENT

As mentioned earlier, the basis of the pharmacological treatment for achieving control and preventing future risks in asthma is the use of an ICS with or without a LABA. However, other medications play an important role, either in the relief of symptoms, such as a SABA, or as an option in the first-line control treatment, and the previous maintenance therapy can even be reintroduced for patients who have not achieved control.

As-needed ICS+SABA

The use of as-needed ICS+SABA is another option recommended for the control treatment in steps 1 and 2 of the 2019 GINA.[1] This recommendation is based on studies[60-62] of patients in step 2 who used an ICS and a SABA in separate or combined inhalers, which showed that this strategy significantly reduced exacerbations when compared with the use of a SABA

Table 2. Equivalence of doses of inhaled corticosteroids licensed for use in Brazil.[a]

ADULTS AND ADOLESCENTS (≥ 12 years of age)				
Corticosteroids	**Type of inhaler**	**Low dose, μg/day[b]**	**Medium dose, μg/day**	**High dose, μg/day[c]**
Beclomethasone dipropionate	DPI, HFA	100-200	> 200-400	> 400
Budesonide	DPI, HFA	200-400	> 400-800	> 800
Fluticasone propionate	DPI, HFA	100-250	> 250-500	> 500
Fluticasone Furoate	DPI	na	100	200
Mometasone Furoate	DPI	110-220	> 220-440	> 440
CHILDREN 6-11 YEARS OF AGE				
Corticosteroids	**Type of inhaler**	**Low dose, μg/day[b]**	**Medium dose, μg/day**	**High dose, μg/day[c]**
Beclomethasone dipropionate	DPI, HFA	50-100	> 100-200	> 200
Budesonide	DPI	100-200	> 200-500	> 500
	Vials	250-500	> 500-1,000	> 1,000
Fluticasone propionate	HFA	100-200	> 200-500	> 500
	DPI	100-200	> 200-400	> 400
Mometasone Furoate	DPI	110	≥ 220 < 440	≥ 440
CHILDREN < 6 YEARS OF AGE				
Corticosteroids	**Type of inhaler**	**Low dose, μg/day**	**Age**	
Beclomethasone dipropionate	HFA	100	≥ 5 years	
Budesonide	Vial	500	≥ 6 months	
Fluticasone propionate	HFA	50	≥ 4 years	
Mometasone Furoate	DPI	110	≥ 4 years	

DPI: dry powder inhaler; HFA: hydrofluoroalkane, pressurized inhaler; and na: not available. [a]Dose labeled on the medication box. [b]Standard dose to start and maintain the treatment of most patients.[2,9] [c]Greatly increases the frequency and intensity of systemic adverse effects.

alone, in addition to reducing the risk of excessive SABA use, given that adherence to the ICS alone is low in this relatively asymptomatic population. In addition, the ICS-SABA combination is available in many countries, including Brazil, and is more affordable than is the ICS-LABA combination.

Montelukast

Montelukast is a leukotriene receptor antagonist that acts by blocking bronchoconstriction and reducing airway inflammation. Although the effect of montelukast is not inferior to that of an ICS in the control of asthma,[63] it is less effective in reducing the risk of exacerbations. Montelukast combined with an ICS is included as another treatment option in GINA steps 2-4.[1] Montelukast can also be added to the ICS-LABA combination in order to improve asthma control (step 4) and may be an alternative to the use of a SABA in exercise-induced asthma, being used daily or intermittently.[64] The recommended daily dose of montelukast is 4 mg for asthma patients from 2 to 5 years of age, 5 mg for those from 6 to 14 years of age, and 10 mg for those ≥ 15 years of age.[65,66]

SABA AS RESCUE MEDICATION

In step 1 of the GINA treatment, the use of SABA combined with ICS is an alternative to the use of as-needed low-dose ICS+formoterol. In patients using an ICS alone or fixed-dose ICS+LABA, a SABA is indicated as an optional rescue medication in all of the GINA asthma treatment steps.[1]

The as-needed use of a SABA (always combined with ICS) is effective for the immediate relief of symptoms and for the short-term prevention of symptoms induced by exercise. The frequency of the use of a SABA is one of the parameters that define which maintenance therapy is the most appropriate, and the reduction of its usage is one of the goals of the asthma treatment.[1] The excessive use of SABA (> 3 canisters/year) is associated with an increased risk of exacerbations, and the use of > 1 canister/month is associated with a higher risk of death from asthma.[1]

ASTHMA MANAGEMENT IN CHILDREN 6-11 YEARS OF AGE

With the objective of reducing risk and controlling symptoms, the pharmacological treatment for children 6-11 years of age with asthma is basically similar to that employed for adolescent and adult asthma patients (Figure 2). Except for a few studies on the particulars of the safety of corticosteroids, there have been almost no studies on the use of some medications in this age range. As a preferred recommendation in the treatment steps, the main controller medications used (ICS, LABAs, and leukotriene receptor antagonists) are the same for patients ≥ 12 years of age. In recent years, the treatment alternatives for 6- to 11-year-old children with severe asthma have expanded to include omalizumab (an anti-IgE monoclonal antibody), as well as, more recently, tiotropium (an anticholinergic) and mepolizumab (an anti-IL-5 monoclonal antibody). The following are the particular characteristics of

pharmacological treatment in this age group, considering the GINA treatment steps[1]:

- Step 1: A SABA should be used as needed and combined with an ICS when symptoms occur.[61]
- Step 2: The preferred treatment is continuous, low-dose ICS therapy.
- Step 3: The preferred treatment is moderate-dose ICS therapy or low-dose ICS therapy combined with a LABA.
- Step 4: Patients with uncontrolled disease in step 3 should maintain the controller medication and be referred to a specialist, who will evaluate the need to increase the ICS dose or to add tiotropium.
- Step 5: Tiotropium, omalizumab, and mepolizumab are options for this age group, according to the asthma phenotype and the clinical experience of the specialist. After many years as a first option, the use of low-dose oral corticosteroids (OCS) has become the last option for combination at this treatment step.

Of all adverse ICS effects, growth, bone metabolism, and the risk of fractures in children and adolescents have been the main focus of studies in recent years. However, severe uncontrolled asthma can also impair growth, and studies to date have shown that regular ICS use in children causes only a transitory reduction in the growth rate and appears to result in only a slight reduction in their final stature.[67] Osteopenia and the risk of fractures are associated with more frequent use of systemic corticosteroids (oral or injectable).[68,69] Therefore, the benefits of ICS in asthma control outweigh its potential adverse effects on growth.

ASTHMA MANAGEMENT IN CHILDREN < 6 YEARS OF AGE

A diagnosis of asthma is more likely in children who present cough, recurrent wheezing (during sleep or prompted by triggers such as physical activity, laughing, crying, or exposure to tobacco or pollution), respiratory distress (when exercising, laughing, or crying), or a reduction in physical activity, as well as in those who have a parent with asthma, those who have a history of other allergies (atopic dermatitis or rhinitis), and those in whom the therapeutic test with low-dose ICS is positive (clinical improvement after 2-3 months of treatment and loss of control when the treatment is stopped).[1]

Maintenance therapy

The goal of maintenance therapy is to achieve asthma control, maintaining the normal activity of the child with a minimum of medication. It also seeks to reduce crises, allow healthy lung development, and avoid side effects.

Preventive treatment should be initiated if the clinical presentation is consistent with asthma and the symptoms are uncontrolled. If the diagnosis is uncertain, a SABA should be used as rescue medication. However, if the episodes of wheezing become recurrent, a therapeutic test with low-dose ICS is recommended.

The treatment should be administered via a pressurized, metered-dose inhaler with a spacer and a mask (for children < 4 years of age), although an inhaler without a mask should be used in older children. Those responsible for the child should be instructed in the correct use of the inhaler and the proper inhalation technique. The dose equivalence of the ICS in this age group is described in Table 2. The treatment should be adjusted in accordance with the level of asthma control (Figure 3).

The response to treatment should be evaluated. In the absence of a response, the treatment should be discontinued and alternative diagnoses should be considered. If satisfactory asthma control is not achieved with moderate-dose ICS combined with montelukast, adding a LABA could be considered. We emphasize that there have been very few studies evaluating the efficacy and safety of the use of this combination in this age group.[47,70,71] In this situation, referring the patient to a specialist should be considered.

Rescue therapy

Crises should be treated with 200 µg of albuterol or equivalent, with the use of a spacer, with or without a mask. The same dose should be administered every 20 min, if necessary. If using more than 6 puffs of albuterol in the first 2 h, ipratropium bromide (80 µg, or 250 µg by nebulization) can be added every 20 min to 1 h[72] In the absence of a satisfactory response, it is recommended that the patient seek prompt medical treatment.

The routine use of OCS during crises is not recommended and should be restricted to crises that require emergency care. In such cases, the physician should prioritize low doses and treatment for the least number of days possible (1-2 mg/kg per day of prednisone/prednisolone for 3-5 days, with maximum doses of 20 mg per day for children ≤ 2 years of age and 30 mg per day for children > 2 and ≤ 5 years of age). After emergency consultation, the patient should be reevaluated at 24-48 h and within 3-4 weeks thereafter.

MANAGEMENT OF SEVERE ASTHMA

Severe asthma is defined as that which remains uncontrolled with maximum optimized treatment or that needs this treatment to prevent the disease from becoming uncontrolled (in an attempt to reduce the dose of ICS or OCS), despite the suppression or minimization of factors that impair asthma control.[73,74] The maximum treatment means using high doses of ICS and a second controller medication within the previous year or the use of OCS on ≥ 50% of the days in the last year.[73]

Severe asthma is a subgroup of difficult-to-control asthma. In a recent study, Hekking et al.[32] estimated that the prevalence of difficult-to-control asthma is 17.4% but that only 3.6% of the patients with difficult-to-control asthma have severe asthma.[74]

Therefore, the diagnosis of severe asthma is made retrospectively. The suppression or minimization of modifiable factors associated with the lack of control is not always possible, which may complicate the diagnosis of severe asthma.

Tiotropium

Tiotropium bromide, at a dose of 5 µg/day, is recommended as adjuvant therapy for patients with asthma aged > 6 years with uncontrolled asthma in the GINA steps 4 and 5.[1] A systematic review showed that the combination of tiotropium and IC+LABA improves lung function and reduces the rate of exacerbations.[75]

Although there have been no studies comparing the use of tiotropium with that of biologic agents or establishing what the preferred medication would be following the addition of the various controller medications in GINA step 5, for reasons of availability, the use of tiotropium could be recommended over that of a biologic agent.[76] In patients with asthma that is less severe (step 3), tiotropium can be an alternative to the use of LABAs, which can increase the risk of adverse events (when they are not well tolerated by the patients) or can be ineffective.[77] Reports of adverse effects such as dry mouth and urinary retention are typically associated with anticholinergic drugs but are infrequent in patients with asthma.[78]

Omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody,[79] approved for use in Brazil and recommended in GINA step 5 for the treatment of severe allergic asthma. One review of the literature,[80] evaluating 25 RCTs involving patients with moderate to severe allergic asthma, showed that omalizumab, when compared with a placebo, reduced the exacerbations by approximately 25%, decreased the number of hospitalizations, and allowed a slight reduction in the dose of ICS. A systematic review of 42 real-life studies,[81] two of which were conducted in Brazil,[82,83] showed that omalizumab improved asthma control, reduced the number of emergency room visits/hospitalizations, and allowed the use of lower doses of OCS and ICS.

Omalizumab is recommended for patients with severe asthma ≥ 6 years of age. The dose varies depending on patient weight (20-150 kg) and total serum IgE (30-1,500 IU/mL) and is administered subcutaneously every 2 or 4 weeks. Response to this treatment has no predictor or single outcome. We recommend evaluating its effectiveness based on clinical outcomes after its use for 16 weeks.[84] It is generally well tolerated. Despite the risk of anaphylaxis being low (0.07-0.14%), patients should receive the medication and be monitored in an environment with adequate equipment for cardiopulmonary resuscitation after the administration of each dose.[84]

Mepolizumab

Mepolizumab is a humanized monoclonal antibody that inhibits IL-5 from binding to its receptors in the eosinophils, which consequently reduces eosinophilic inflammation.[85]

Several RCTs[86-91] and a meta-analysis[92] showed that the addition of mepolizumab to the treatment for severe asthma relieves symptoms, improves lung function, reduces exacerbations, has an OCS-sparing effect in asthma patients who are dependent on OCS, and produces a significant, clinically relevant improvement in quality of life.

In Brazil, mepolizumab is recommended for the treatment of severe eosinophilic asthma in patients over the age of 6 years in GINA step 5.[74,91] Studies of mepolizumab have characterized eosinophilia in peripheral blood as ≥ 150 cells/µL at the time of evaluation or ≥ 300 cells/µL in the last 12 months.[74,91]

Mepolizumab should be used subcutaneously at a dose of 100 mg every 4 weeks and rarely causes hypersensitivity reactions.

Benralizumab

Benralizumab is a humanized IgG1-kappa monoclonal antibody, recommended as an add-on therapy in patients with severe eosinophilic asthma. When it binds to the IL-5 receptor alpha, it leads to apoptosis of eosinophils, resulting in rapid and almost complete depletion of serum levels of eosinophils.[93]

Several RCTs[94-97] and one meta-analysis[92] showed that the addition of benralizumab to the usual treatment in GINA step 5 reduces the rate of exacerbations and the need for chronic OCS use, with improvement of symptoms and lung function. Those studies defined severe eosinophilic asthma as ≥ 300 cells/µL in the peripheral blood.

In Brazil, benralizumab is recommended for patients above the age of 18 years in GINA step 5[1,74] and is available as a single-dose syringe. The recommended dose is 30 mg administered subcutaneously, every 4 weeks for the first three doses, and every 8 weeks thereafter. Benralizumab seldom causes hypersensitivity reactions.

Low-dose OCS

The use of OCS is recommended as an add-on therapy in patients with severe uncontrolled asthma in GINA step 5.[1,74] Before starting the maintenance OCS, it is essential to review all conditions that can be associated with a lack of response to the asthma treatment: other medications in use, adherence, inhalation technique, comorbidities, and exposures. Its prolonged use can cause severe adverse effects, including growth retardation in children, glaucoma, cataracts, diabetes mellitus, osteoporosis, infections, and blockage of the hypothalamic-pituitary-adrenal axis.[73,74,98]

Some strategies, such as the use of OCS at low doses (≤ 7.5 mg of prednisolone) or on alternate days, can minimize the risk of adverse effects. After the prolonged use of OCS (for > 3 months), the patient should be monitored permanently, due to the risk of acute adrenal insufficiency in cases of trauma, acute

disease, or surgery. In those cases, corticosteroid replacement may be necessary.[1,73,74] The use of low-dose OCS (with or without an antifungal) can also be recommended for the treatment of allergic bronchopulmonary aspergillosis.[74]

Azithromycin

The use of azithromycin for treating asthma is controversial. A systematic review of the literature in 2015 evaluated all clinical trials involving azithromycin and concluded that there was no evidence that its use would be better than a placebo for the majority of clinical outcomes.[99] However, a recent RCT showed improvement of asthma control and reduction of eosinophilic and noneosinophilic asthma exacerbations with the use of oral azithromycin at a dose of 500 mg three times per week for 12 months.[100] In addition, this use of azithromycin is off-label and may be associated with adverse effects such as ototoxicity, cardiac arrhythmia, and increased QT interval, as well as increased drug resistance of bacteria. Further studies are required to prove its efficacy and safety in the control of asthma.[1]

Other medications for the treatment of severe asthma

Dupilumab is a monoclonal antibody against the IL-4 receptor alpha,[101] recommended for the treatment of severe asthma of the Th2-high subtype, characterized by elevated eosinophil counts or fractional exhaled nitric oxide levels, in patients > 12 years of age. When it binds to the IL-4 receptor, dupilumab also inhibits the activity of IL-13, another important player in this asthma phenotype. Dupilumab reduces asthma exacerbations, allows a gradual reduction in the use of OCS, and improves lung function.[101-105] It is administered subcutaneously, at a recommended dose of 400 mg initially, followed by 200 mg on alternate weeks. For patients using OCS or with comorbidities (atopic dermatitis, nasal polyposis, or eosinophilic esophagitis), the recommended dose is 600 mg initially, followed by 300 mg every 2 weeks. In Brazil, dupilumab is already used for atopic dermatitis and should soon be approved by the Brazilian National Health Oversight Agency for clinical use in asthma.

Reslizumab is an anti-IL-5 monoclonal antibody for the treatment of severe, uncontrolled, eosinophilic asthma (GINA step 5), although it has yet to be approved for clinical use in Brazil.[106] Reslizumab is administered intravenously in adults (≥ 18 years of age) with blood eosinophil counts > 400 cells/μL at a dose of 3 mg/kg of body weight for 25-50 min every 4 weeks, resulting in a reduction of symptoms and exacerbations and an improvement in lung function.[92,106]

OTHER APPROACHES TO ASTHMA MANAGEMENT

Vaccines

In Brazil, influenza vaccinations are indicated for patients with asthma[107] because the virus is associated with increased morbidity in such patients.[108-110] Two meta-analyses concluded that, although there is evidence that vaccinating these individuals can prevent infection and asthma exacerbations, the quality of the evidence is low.[109,110] There are no contraindications to the vaccination of asthma patients. Those with only mild reactions to eggs (urticaria or angioedema) can be vaccinated at a primary health care clinic. Patients with a history consistent with or suspicious for anaphylactic reactions to eggs should be vaccinated in a setting suitable for the treatment of a possible anaphylactic reaction.[111,112]

Asthma patients, especially those with severe asthma, are more susceptible to pneumococcal infections.[113,114] Pneumococcal vaccines (the 23-valent pneumococcal polysaccharide vaccine and the 10-valent pneumococcal conjugate vaccine) are available through the SUS for individuals with persistent moderate or severe asthma,[107] as is the 10-valent pneumococcal conjugate vaccine for children up to 1 year and 11 months of age. The *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) recommends the sequential use of pneumococcal vaccines: the 13-valent pneumococcal conjugate vaccine followed by the 23-valent pneumococcal polysaccharide vaccine 6 months later.[115]

Immunotherapy

Immunotherapy administered subcutaneously or sublingually is an option for patients who have asthma with a prominent allergic component. A meta-analysis of 98 studies[116] found that immunotherapy was effective in reducing the symptoms and the need to use controller medication, regardless of patient age and duration of treatment, in individuals with mild-to-moderate asthma who are monosensitized for house dust mites. The benefit is less robust in individuals with severe asthma who are polysensitized. The risk of adverse systemic reactions was found to be higher after subcutaneous administration of immunotherapy in comparison with placebo. Another meta-analysis[117] reported modest benefits of sublingual immunotherapy in patients with mild-to-moderate asthma.

ACTION PLAN

All asthma patients should have a written action plan. This is an important tool in the treatment of asthma to help patients recognize and adjust the treatment early, whenever control becomes difficult. The action plan should be individualized and developed in partnership with the patient. It involves education to monitor the symptoms, early recognition of an exacerbation, and strategies that will guide the patient for home treatment of crises.

The action plan should be divided into four topics: day-to-day treatment of controlled asthma; when, how, and for how long to use rescue medication and to increase the controller medication dose; when to use an OCS; and when to seek emergency medical

care.[118] In addition, the action plan should include the definitions of asthma control levels throughout. Monitoring strategies and action plans are effective in the control of asthma.[119]

SABA as rescue medication when using an ICS alone or fixed-dose ICS+LABA

The repeated use of SABA for ≥ 2 consecutive days is a warning sign and indicates the need to reintroduce or reassess and adjust the controller medication. A SABA should not be used in isolation.[1] If the patient is using an ICS alone or fixed-dose ICS+LABA and SABA as rescue medications, the action plan should specify the maximum daily dose of SABA and the number of days it should be used before the patient modifies the treatment or seeks routine or emergency medical care. The action plan should indicate that the recommended dose of SABA is from one to two doses inhaled via a spacer, if needed, and may be repeated every 20-30 min (maximum of three doses).

Increasing the ICS dose when using an ICS alone or fixed-dose ICS+LABA

The ICS dose can be doubled when asthma symptoms worsen, requiring repeated doses of SABA for 1-2 days. The ICS should be reintroduced for patients who have stopped using it. For patients using an ICS alone, the dose should be doubled. For patients using fixed-dose ICS+LABA, the highest dose of the combination should be used. If the patient is already taking the highest dose of the ICS alone, a LABA should be added. For patients using fixed-dose ICS+LABA, the ICS dose should be increased to the highest dose for this combination.[1,3,4]

Increasing the ICS dose when using ICS+formoterol as maintenance and rescue medications

For patients using ICS+formoterol as maintenance and rescue medications, the action plan must contain a daily fixed dose every 12 h and additional doses when there are signs of uncontrolled asthma (up to 6 extra doses of 6 µg of formoterol). The maximum recommended dose of formoterol is 72 µg/day.[41-44,55]

Guidelines for the use of OCS

The action plan should contain guidelines for when and how to start a course of OCS. A dose of up to 40-50 mg/day for 5-7 days is recommended for patients with no improvement in asthma control 48 h after using a SABA, with worsening of lung function, or with a more severe exacerbation. For children, the recommendation is a single dose of 1-2 mg/kg of body weight per day for 3-5 days. Patients should be advised of the adverse effects of using an OCS. It is unnecessary to reduce the dose of the OCS when the duration of treatment is less than 2 weeks.

FINAL CONSIDERATIONS

Asthma is a complex, heterogeneous disease associated with high morbidity and high utilization of health resources. The management of asthma has changed considerably in recent years. The SBPT regularly publishes guidelines, standards, and position papers on topics relating to the field. In the present manuscript, prepared by 22 pulmonologists and pediatric pulmonologists, with extensive experience in this area, recommendations for the pharmacological treatment of asthma are made and the latest international guidelines are adapted for use in Brazil.

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Pulmonary manifestations of dengue

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TO THE EDITOR:

Dengue is an arthropod-borne viral disease transmitted to humans through the bites of infected female mosquitoes of the *Aedes* genus. The dengue virus (DENV) belongs to the Flaviviridae family, and humans can be infected with any of the four antigenically distinct serotypes (DENV 1-4).[1-7] The prevalence of DENV infection has increased dramatically in recent decades; the disease is now endemic in > 100 countries worldwide. The global resurgence of dengue is thought to be due to the failure to control *Aedes* spp. populations, uncontrolled urbanization, population growth, climate change, and increasing numbers of international travelers.[1,2,4,5,7] In Brazil, the number of cases of dengue fever reported in January-August 2019 was approximately 600% higher than that reported during the same period in 2018. As of August 2019, the disease had caused 591 deaths, compared with only 141 for the same period in 2018.[8]

According to the 2009 World Health Organization guidelines,[2] patients with dengue are categorized as having the non-severe form (subdivided into those with warning signs and those without) or the severe form. Patients with non-severe dengue without warning signs are defined as those who live in or have travelled to dengue-endemic areas and have fever, together with at least two of the following: nausea, vomiting, rash, pain, leukopenia, and positive tourniquet test results. Patients with non-severe dengue with warning signs are defined as those who present with all of the above, plus any of the following additional symptoms: abdominal pain or tenderness, persistent vomiting, fluid accumulation (pleural effusion or ascites), mucosal bleeding, lethargy, restlessness, liver enlargement > 2 cm, and an increase in hematocrit concurrent with a rapid decrease in the platelet count. Severe dengue is characterized by at least one of the following: severe plasma leakage leading to shock, with or without fluid accumulation with respiratory distress, and severe bleeding or severe involvement of organs (liver, central nervous system, heart, or other).[1-4,7]

Dengue has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe, lethal manifestations. The disease usually presents as acute fever with headache, rash, myalgia, arthralgia, retro-orbital pain, prostration, lymphadenopathy, and dry cough. Hemorrhagic manifestations in patients with dengue are usually mild, most commonly consisting of scattered tiny petechiae on the skin or submucosa and ecchymoses. Variable frequencies of respiratory symptoms have been reported in patients with dengue; the symptoms are generally mild and affect mainly the upper airway.[5,7,9-11] Pulmonary complications are less common and can present as pleural effusion, pneumonitis, noncardiogenic pulmonary edema, acute respiratory distress syndrome, and pulmonary hemorrhage. Such complications coincide with capillary leak syndrome and thrombocytopenia. Dyspnea may occur due to pleural effusion (most frequently), acute respiratory distress syndrome, pulmonary hemorrhage, pneumonia, or shock. Diffuse alveolar hemorrhage is rare, and is typically related to severe—often fatal—forms of the disease. Hemoptysis has been reported in 1.4% of DENV infections.[5-7,9,10]

The early diagnosis of dengue can be established provisionally by clinical observation and readily available laboratory tests. In general, laboratory findings of dengue include neutropenia followed by lymphocytosis, the presence of atypical lymphocytes, and moderate to marked thrombocytopenia with concurrent hemoconcentration.[5,7,11]

Diagnostic options include assays to detect DENV, its components (genome and antigen), or the host response to the virus. Laboratory confirmation can be made by detecting the viral genomic sequence through RT-PCR or the presence of DENV nonstructural protein 1 (NS1) antigen though immunoassay in a single acute-phase serum specimen obtained early (less than five days after fever onset). During the febrile phase, the detection of viral nucleic acid in serum by RT-PCR or of DENV-expressed soluble NS1 by ELISA or the lateral-flow rapid test is sufficient for a confirmatory diagnosis. Therefore, less than five days after fever onset, RT-PCR is indicated, and serology (IgM ELISA) should be performed only after day 5. A finding of IgM seroconversion (≥ 4-fold increase in the antibody titer) between paired samples is considered to be confirmatory; IgM detection in a single specimen from a patient with a clinical syndrome consistent with dengue is used widely to establish a presumptive diagnosis.[2,4,7,9]

The most commonly observed chest imaging finding in dengue is pleural effusion, which is often bilateral. When unilateral, it usually occurs on the right. Parenchymal abnormalities, including ground-glass opacities and consolidations, are less common, have no specific distribution pattern, and can be accompanied by interlobular septal thickening and nodules, representing edema or pulmonary hemorrhage (Figure 1).[6,7,9-11]

We had the opportunity to review the CT findings of 9 patients with severe dengue confirmed by serology. The most common CT findings were multifocal ground-glass opacities, which were seen in 8 patients (88.9%). A predominance of central (perihilar) lung involvement was

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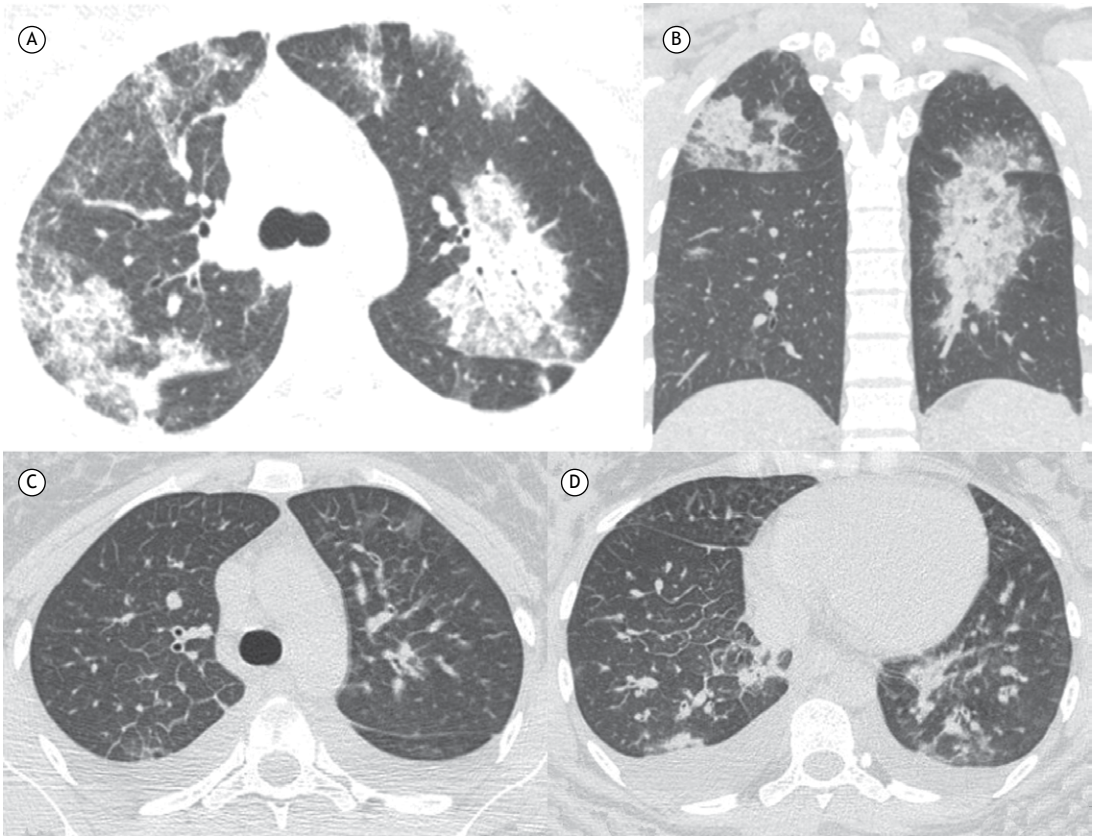

Figure 1. Two patients diagnosed with dengue. In A and B, a 37-year-old woman with severe dengue and pulmonary hemorrhage. Axial CT scan (A) and coronal reconstruction (B), showing bilateral multifocal areas of consolidation and ground-glass opacity. In C and D, a 51-year-old woman with severe dengue and findings of pulmonary edema. Axial CT scans of the upper and lower lobes (C and D, respectively), showing bilateral peribronchovascular and interlobular septal thickening, together with multifocal areas of mild consolidation and ground-glass opacity in both lungs. Note also the bilateral pleural effusion.

observed in 4 patients (44.4%). Four patients (44.4%) also had areas of consolidation. The consolidations were accompanied by ground-glass opacities in 3 patients (33.3%); consolidations only were observed in 1 (11.1%). A crazy-paving pattern and smooth interlobular septal thickening were observed in 1 patient (11.1%) each. Bilateral pleural effusion was observed in 5 patients (55.6%). In all of the patients, the abnormalities were bilateral and diffuse (Figure 1).

Drawing clinical and radiological distinctions between dengue and other infections that cause diffuse pulmonary hemorrhage may be challenging. In immunocompetent patients, the most important infectious diseases for differential diagnosis include influenza A (H1N1), leptospirosis, malaria, and hantavirus pulmonary syndrome. Those conditions can occur in similar epidemiological contexts, increasing the diagnostic challenge.[6,7]

Morphologically, lung tissue from patients with dengue shows interstitial edema and pneumonia, accompanied by focal or diffuse zones of alveolar congestion/hemorrhage and an increased number of alveolar macrophages, as well as the recruitment of platelets, mononuclear cells, and polymorphonuclear cells. Hyaline membranes may also be found.[6,7,9,11]

No specific treatment for dengue is available. However, careful clinical management frequently saves the lives of patients with pulmonary hemorrhage. With appropriate intensive supportive therapy, mortality may be reduced to < 1%.[2,5,7]

In conclusion, lung abnormalities are uncommon in dengue, and imaging findings probably reflect increased vascular permeability. Dengue should be considered in the differential diagnosis of patients with fever, hemoptysis, and diffuse pulmonary infiltration. The most common imaging findings in dengue are bilateral areas of ground-glass opacity or consolidation and bilateral pleural effusions. Recognition of these findings may help clinicians initiate prompt treatment and prevent mortality.

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Assessment of theoretical and practical knowledge of asthma among guardians of children treated in primary care

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TO THE EDITOR:

Asthma is a highly prevalent chronic respiratory disease and constitutes a serious global public health problem. Its management is related to symptom control. Asthma control requires knowledge of the disease, because children depend on their guardians for asthma management.[2] Studies have demonstrated that only 50% of patients achieve symptom control through treatment adherence as instructed by a health care team.[3] Inhaled medication use, with correct inhaler technique, reevaluation visits by a multidisciplinary team, and changes in lifestyle habits are strategic measures in the treatment of asthma in childhood.[4]

Therefore, a cross-sectional study was designed with the objective of assessing the health literacy and asthma knowledge levels of guardians of children and adolescents (1-17 years old) diagnosed with the disease and registered in the *Rede Bem-Estar* (Well-being Network) in the city of Vitória, Brazil. The study was approved by the local research ethics committee (Protocol no. 2.257.264), and written informed consent was obtained from all participants. Patient selection included five health care facilities that were chosen by convenience sampling. We excluded patients with cognitive or motor limitations or with other chronic diseases that could compromise the evaluation of health control, attitudes, and practices.

The diagnosis of asthma was made by a pediatrician working in the municipal health care system in the city of Vitória, in accordance with the tenth revision of the International Classification of Diseases (code J45). Patient follow-up in primary care is carried out jointly by a Family Health Program physician and a specialist physician (pediatrician).

Patients' guardians were administered a clinical questionnaire and a socioeconomic classification questionnaire.[5] For assessment of asthma control, they completed the Global Initiative for Asthma questionnaire,[1] which categorizes asthma control levels (as controlled, partly controlled, and uncontrolled). For assessment of disease knowledge, they were administered a specific questionnaire on knowledge of pediatric asthma (Newcastle Asthma Knowledge Questionnaire)[6] and a health literacy questionnaire (Short Assessment of Health Literacy for Portuguese-speaking Adults).[7] For assessment of treatment attitudes and practices, they were administered a theoretical questionnaire and underwent observational practice analysis regarding the specific management for treating asthma. For analysis of understanding of prescription instructions, the guardians were assessed as to the type of prescription (preventive or rescue) and their understanding of the prescription instructions; their level of understanding was classified as adequate or inadequate. For the purpose of establishing cut-off points for the questionnaires, scores of at least 70% (≥ 7 points) were considered acceptable. For the purpose of statistical analysis, the chi-square test was used for nominal variables, and ANOVA with the Bonferroni post hoc test was used for scalar variables.

A total of 120 children with asthma, with a mean age of 6.3 ± 3.9 years, participated in the study. Their guardians had a mean age of 39.9 ± 13.0 years, and it was the mothers who predominantly took their children to medical appointments (n = 94; 78.3%). A total of 45.0% of the guardians had completed high school, and 48.3% belonged to the middle socioeconomic class (class C).

Comparison of results by asthma control group (Table 1) showed significant differences for the following variables: symptoms of chest tightness ever ($p = 0.02$); wheezing or shortness of breath at rest ($p = 0.02$); hospitalization for asthma ($p = 0.01$); and school absenteeism ($p = 0.01$). In addition, the results regarding asthma treatment in the past 12 months showed that the totally controlled asthma group had the highest proportion of patients receiving continuous treatment ($p < 0.01$) and the lowest proportions of patients using oral corticosteroids ($p = 0.01$) and bronchodilators ($p = 0.01$).

In the assessment of inhalation techniques, the results revealed poor theoretical knowledge of the techniques, with no differences between the groups ($p = 0.08$). However, the frequency of guardians with adequate practical knowledge of inhalation techniques was significantly higher in the totally controlled asthma group than in the other groups ($p < 0.01$). In the assessment of prescription literacy and understanding of prescription instructions and type of treatment, the results showed that guardians of children with greater asthma control have a better understanding of the disease. In the assessment of health literacy, there

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Table 1. Asthma diagnoses, asthma symptoms, and asthma treatment, by asthma control classification.[a]

Variable	Asthma			p
	Uncontrolled (n = 75)	Partly controlled (n = 11)	Totally controlled (n = 34)	
Diagnosis of rhinitis	59 (78.7)	9 (81.8)	32 (94.1)	0.13
Diagnosis of atopy	42 (56.0)	7 (63.6)	20 (58.8)	0.88
Asthma symptoms (ever)				
Woken up with shortness of breath	73 (97.3)	11 (100.0)	34 (100.0)	0.55
Woken up with chest tightness	43 (57.3)	11 (100.0)	23 (67.6)	0.02**
Asthma symptoms (in the past 12 months)				
Wheezing/shortness of breath during exercise	47 (62.7)	9(81.8)	18 (52.9)	0.22
Wheezing/shortness of breath at rest	66 (88.0)	10 (90.9)	23 (67.6)	0.02*
Hospitalization for asthma	43 (57.3)	9 (81.8)	12 (35.3)	0.01**
Only once	40 (93.0)	8 (88.9)	12 (100.0)	0.01**
Twice or more	3 (7.0)	1(11.1)	0 (0.0)	
School absenteeism in the last school year	70 (93.3)	11 (100.0)	26 (76.5)	0.01*
One full week	6 (8.0)	2 (18.2)	5 (14.7)	0.01*
Two full weeks	24 (32.0)	4 (36.4)	12 (35.3)	
More than two weeks	40 (53.3)	5 (45.5)	9 (26.5)	
Asthma treatment (in the past 12 months)				
Has a prescription for medication to treat asthma attacks	70 (93.3)	11 (100.0)	34 (100.0)	0.21
Continuous treatment	41 (54.7)	9 (81.8)	34 (100.0)	< 0.01**
Takes treatment before exercise	43 (57.3)	8 (72.7)	14 (41.2)	0.13
Treatment with inhaled corticosteroids	70 (93.3)	11 (100.0)	34 (100.0)	0.21
Treatment with oral corticosteroids	63 (84.0)	9 (81.8)	20 (58.8)	0.01*
Treatment with bronchodilators	75 (100.0)	11 (100.0)	30 (88.2)	0.01*
Treatment with leukotriene receptor antagonists	3 (4.0)	0 (0.0)	3 (8.8)	0.41
Recieves medication via the public health care system	74 (98.7)	11 (100.0)	34 (100.0)	0.74
Uses a spacer for the treatment	59 (78.7)	11 (100.0)	29 (85.3)	0.20
Uses a commercial spacer	58 (98.3)	11 (100.0)	29 (100.0)	0.71

[a]Values expressed as n (%). *p < 0.05 between the totally controlled asthma group and the other groups. **p < 0.05 between the three asthma control groups.

were no statistically significant differences between the asthma control groups. In contrast, in the assessment of asthma knowledge, values were lower in the partly controlled asthma group than in the other groups (p = 0.02). With regard to prescription literacy and understanding of prescription instructions and type of treatment, we found that greater understanding of the procedures for proper treatment indicates better disease control scores.

Another relevant finding concerns asthma control through continuous, preventive treatment. All patients with totally controlled and partly controlled asthma had prescriptions for medication to treat asthma attacks. In addition, adherence to continuous treatment was better in the totally controlled and partly controlled asthma groups (100.0% and 81.8%, respectively). However, in the uncontrolled asthma group, 54.7% of the patients were adherent to continuous treatment, and a predominant number of patients used inhaled and oral corticosteroids.

The present study demonstrates that the vast majority of children with asthma do not have controlled disease, and inadequate asthma control is due to lower use of controller medication. In addition, rescue medications and oral corticosteroids were demonstrated to be very frequently used by patients with partly controlled or uncontrolled asthma. Another important factor concerns prescription literacy and understanding of prescription instructions and type of treatment: greater understanding of the procedures for proper treatment translates to better disease control.

Limitations to this study include the type of design (cross-sectional) with one-time assessment, the non-probabilistic (convenience) sampling, and the age range studied.

Finally, our findings underscore the need for improving asthma knowledge in the groups studied in order to increase disease control through parent and patient educational programs that are central to and effective in consolidating public policies aimed at health promotion.

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Influence of a heat and moisture exchanger with a microbiological filter on measurements of maximal respiratory pressures and vital capacity in patients with COPD

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TO THE EDITOR:

COPD is characterized by persistent respiratory symptoms such as dyspnea, which contributes to decreased exercise tolerance. One of the main mechanisms involved is respiratory muscle dysfunction.[1] Therefore, changes in lung volumes and capacities, especially reduced VC, can be observed in patients with COPD, as can respiratory muscle weakness.[2]

The measurement of VC and respiratory pressures (MIP and MEP) is performed using a spirometer (Figure 1A) and a manometer (Figure 1C), respectively. These devices are cleaned only externally, which may contribute to the increased incidence of infections, given that no device is utilized to filter the air inhaled and exhaled by patients during routine evaluations.[3] Therefore, a viable alternative would be to use heat and moisture exchangers (HMEs) on such equipment.

A hydrophobic HME contains an inline, disposable, hygroscopic, bacteriostatic sponge (microbiological filter, Figures 1B and 1D) that reduces device contamination, thus protecting patients from microbial contamination.[4]

Lucato et al.[5] demonstrated that the dead space volume and resistance caused by the addition of an HME did not change the VC or respiratory muscle strength values in volunteers evaluated during spontaneous breathing. To our knowledge, there have been no studies aimed at determining whether the addition of a microbiological filter has a relevant impact on those variables in patients with impaired pulmonary function. However, such studies are important because it has been reported that the use of an HME may lead to increased pulmonary resistance,[6] which can cause problems in patients with COPD.

The objective of the present study was to determine whether the use of an HME with a microbiological filter alters maximal respiratory pressures or VC in patients with COPD.

We conducted a cross-sectional study in which the start sequence of the evaluation (presence or absence of an HME) was randomized, including 16 patients with COPD undergoing treatment in the cardiopulmonary and metabolic rehabilitation sector of a teaching clinic. The mean FEV_1 in those patients was 36.01 ± 10.56% of the predicted value and the mean FEV_1/FVC ratio was 54.29 ± 10.01% of the predicted value. The sample size was determined by convenience sampling, which explains the small number of patients and may be a limitation of the study. This study was approved by the Research Ethics Committee of the *Centro Universitário São Camilo* (Ruling no. 2,075,696), and all participating patients gave written informed consent. The inclusion criteria were having a spirometry-confirmed diagnosis of COPD and having had no exacerbations in the last six months. Patients who had recently undergone thoracic or abdominal surgery were excluded, as were those presenting with facial deformities, cognitive impairment, myopathy, or acute middle ear infection.

The VC, MIP, and MEP were evaluated with and without an HME (Lumiar Bacteriological Filter; Besmed Health Business Corp., New Taipei City, Taiwan), which is indicated for filtering material from room air and gases, thereby reducing the risk of cross contamination. The filter membrane has high (> 99.99%) bacterial filtration efficiency. The HME was positioned between the mouthpiece and the ventilation equipment. For each variable studied, three measurements were obtained. The highest value was considered for the analysis and then compared with the value obtained without the use of an HME in the same patient. We employed a Ferraris Mark 8 spirometer (Ferraris Respiratory Europe, Hertford, UK) and a Ger-Ar manometer (Ger-Ar-SP Com. Equip. Ltda., São Paulo, Brazil).

The numerical data are expressed as mean and standard deviation and tested for normality using the Shapiro-Wilk test. For comparisons between the two groups—without an HME (conventional method) and with an HME—in terms of the evaluations of VC, MIP, and MEP, we used paired t-tests. The SigmaStat program, version 11.0 (Systat Software, Inc., San Jose, CA, USA) was used, and the level of statistical significance was set at $p < 0.05$.

We selected 16 patients diagnosed with COPD, of which 11 were male. The mean age, weight, and height were 69.9 ± 7.7 years, 66.0 ± 15.3 kg, and 1.62 ± 0.11 m, respectively, and the mean body mass index was 24.84 ± 5.04 kg/m^2.

There were no significant differences between the conventional method and the method that involves the use of an HME in terms of the MIP (−66.5 ± 6.5 cmH_2O

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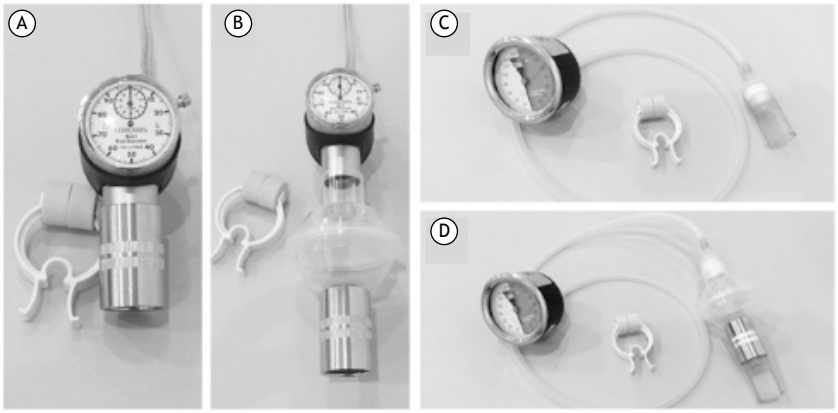

Figure 1. In A, a spirometer as used in the conventional method. In B, a spirometer equipped with a heat and moisture exchanger. In C, a manometer as used in the conventional method. In D, a manometer equipped with a heat and moisture exchanger.

vs. −63.8 ± 5.5 cmH_2O; p = 0.45), MEP (74.4 ± 5.4 cmH_2O vs. 73.4 ± 6.4 cmH_2O; p = 0.61), or VC (2,338.1 ± 211.5 ml vs. 2,350.0 ± 220.5 ml; p = 0.58).

We conclude that the use of an HME does not modify maximal respiratory pressures and VC in patients with COPD.

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Performance of instruments aimed at detecting obstructive sleep apnea syndrome among individuals in Chile

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TO THE EDITOR:

Obstructive sleep apnea syndrome (OSAS) is a common condition, affecting 5-20% of the adult population.[1] Validated diagnostic methods, including polysomnography and home sleep apnea testing (HSAT), are not available at every center, making them poorly accessible in most countries, including Chile.

Clinical prediction models are useful in order to evaluate the population at risk for OSAS.[2] However, it remains unclear which instrument or measure is most effective. It seems to depend on the population studied, and there are no surveys or clinical parameters that have been validated for use in Chile. We designed a study to evaluate the performance of the Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender (STOP-Bang) questionnaire, the Epworth Sleepiness Scale,[3] the snoring scale,[4] the Sleep Apnea Clinical Scale (SACS),[5] and determination of neck circumference in patients suspected of having OSAS in Chile.

Adult patients undergoing sleep studies were prospectively evaluated for clinical suspicion of OSAS and were referred for HSAT. Initially, we evaluated a population of such patients treated at a clinical hospital between 2013 and 2016. We subsequently evaluated a population of such patients treated at a private clinic between 2016 and 2018. Patients suspected of having a sleep disorder other than OSAS were excluded. Before conducting the diagnostic study, we applied the following instruments in all of the patients: the Epworth Sleepiness Scale[3]; the modified snoring scale[6]; the STOP-Bang questionnaire[7]; and the SACS,[5] which is used in order to calculate the adjusted neck circumference (ANC).[2] The study was approved by the local research ethics committee, and all participating patients gave written informed consent.

To perform HSAT, we used a portable sleep monitoring device (Embletta; Natus Medical, Foster City, CA, USA). In accordance with the requirements of the American Academy of Sleep Medicine recommendations for level 3 sleep studies (those involving the use of portable equipment, performed in the home or elsewhere),[8] the tests were performed in the home of the patient, who is given prior instruction. The HSAT results were analyzed manually by a pulmonologist. The patient was categorized as having OSAS if the apnea-hypopnea index (AHI) was ≥ 5 events/h and as having severe OSAS if the AHI was ≥ 30 events/h.

The results are expressed as mean ± standard deviation. Quantitative variables were analyzed by Student's t-tests, and qualitative variables were compared by chi-square tests with confidence intervals (CIs). The result of the HSAT was used as the reference standard, normal HSAT results being used as the reference population.

Discrimination was evaluated by constructing ROC curves for each AHI cutoff point. We calculated the values for sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. The ROC curves were used in order to evaluate tests that presented area under the curve (AUC) > 0.7. Data analysis and recording were performed with Excel 2011 software and with the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

A total of 759 patients were included in the study: 520 in the clinical hospital group; and 239 in the private clinic group. In the clinical hospital group, the AUC for the risk of a diagnosis of OSAS, as determined with the various instruments, were as follows: STOP-Bang questionnaire (AUC = 0.77; CI: 0.70-0.84); SACS (AUC = 0.77; CI: 0.71-0.84); ANC determination (AUC = 0.79; CI: 0.72-0.85); snoring scale (AUC = 0.63; CI: 0.55-0.70); and Epworth Sleepiness Scale (AUC = 0.48; CI: 0.39-0.56). The risk of a diagnosis of severe OSAS was comparable for the SACS, STOP-Bang questionnaire, and ANC determination (AUC = 0.852, 0.837, and 0.863, respectively). As can be seen in Table 1, the best STOP-Bang cutoff score was ≥ 5 points, which had a sensitivity and specificity of 81.7% and 61.4%, respectively, for predicting an AHI ≥ 5 events/h and of 90.0% and 61.4%, respectively, for predicting an AHI ≥ 30 events/h. The best cutoff score on the SACS was ≥ 48 points, which had a sensitivity and specificity of 66.2% and 72.4%, respectively, for predicting a diagnosis of OSAS and of 77.4% and 72.4%, respectively, for predicting a diagnosis of severe OSAS. Finally, the best cutoff ANC was ≥ 40 cm, which had a sensitivity and specificity of 77.3% and 67.2%, respectively, for predicting a diagnosis of OSAS and of 87.5% and 67.2%, respectively, for predicting a diagnosis of severe OSAS. In our validation cohort (private clinic group), contingency tables showed that those cut-off points still had the best sensitivity and specificity for

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Table 1. Performance of instruments employed for predicting an apnea-hypopnea index ≥ 5 events/h or ≥ 30 events/h in patients suspected of having obstructive sleep apnea syndrome in Chile.

Cutoff	Clinical hospital group (n = 520)						Private clinic group (n = 239)					
	Se	Sp	PPV	NPV	LR+	LR−	Se	Sp	PPV	NPV	LR+	LR−
STOP-Bang (AHI ≥ 5 events/h)												
≥ 1 pt	100.0	0.0	88.7	*	1.0	*	100.0	0.0	81.7	*	1.0	*
≥ 2 pts	99.8	1.8	88.8	50.0	1.02	0.13	99.5	2.3	82.0	50.0	1.02	0.22
≥ 3 pts	99.8	8.8	89.6	83.3	1.09	0.03	98.4	20.9	84.8	75.0	1.24	0.07
≥ 4 pts	96.0	22.8	90.7	41.9	1.24	0.18	92.7	41.9	87.7	56.3	1.59	0.17
≥ 5 pts	81.7	61.4	94.3	29.9	2.12	0.3	78.1	72.1	92.6	42.5	2.8	0.3
≥ 6 pts	55.0	80.7	95.7	18.6	2.85	0.56	46.9	88.4	94.7	27.1	4.03	0.6
≥ 7 pts	23.3	91.2	95.4	13.2	2.65	0.84	19.8	97.7	97.4	21.4	8.51	0.82
8 pts	5.1	100.0	100.0	11.9	*	0.95	4.7	100.0	100.0	19.0	*	0.95
STOP-Bang (AHI ≥ 30 events/h)												
≥ 1 pt	100.0	0.0	78.7	*	1.0	*	100.0	0.0	59.0	*	1.0	*
≥ 2 pts	100.0	1.8	78.9	100.0	10.2	0.0	100.0	2.3	59.6	100.0	1.02	0.0
≥ 3 pts	100.0	8.8	80.2	100.0	1.1	0.0	100.0	20.9	64.6	100.0	1.26	0.0
≥ 4 pts	99.0	22.8	82.5	86.7	1.28	0.04	100.0	41.9	71.3	100.0	1.72	0.0
≥ 5 pts	90.0	61.4	89.6	62.5	2.33	0.16	92.1	72.1	82.9	86.1	3.3	0.11
≥ 6 pts	69.0	80.7	92.9	41.4	3.58	0.38	55.6	88.4	87.5	57.6	4.78	0.5
≥ 7 pts	30.5	91.1	92.8	25.9	3.41	0.76	27	97.7	94.4	47.7	11.6	0.75
8 pts	5.7	100.0	100.0	22.4	*	0.94	9.5	100.0	100.0	43.0	*	0.9
SACS (AHI ≥ 5 events/h)												
38-42 pts	98.7	19.0	90.6	64.7	1.22	0.07	98.5	15.9	83.8	70.0	1.17	0.1
43-47 pts	91.6	39.7	92.4	37.1	1.52	0.21	89.2	50.0	88.8	51.2	1.78	0.22
≥ 48 pts	66.2	72.4	95.0	21.2	2.4	0.47	54.9	84.1	93.9	29.6	3.45	0.54
SACS (AHI ≥ 30 events/h)												
38-42 pts	100.0	19.0	82.5	100.0	1.23	0.0	100.0	15.9	62.6	100.0	119.0	0.0
43-47 pts	98.2	39.7	86.1	85.2	1.63	0.05	98.4	50.0	73.5	95.7	1.97	0.03
≥ 48 pts	77.4	72.4	91.4	45.7	2.8	0.31	66.1	84.1	85.4	63.8	4.16	0.4
Neck circumference (AHI ≥ 5 events/h)												
38 cm	86.8	46.6	92.8	30.7	1.62	0.28	92.3	34.1	86.1	50.0	1.4	0.23
39 cm	83.1	60.3	94.3	31.0	2.1	0.28	87.7	40.9	86.8	42.9	148.0	0.3
40 cm	77.3	67.2	94.9	27.1	2.36	0.34	81.5	59.1	89.8	41.9	1.99	0.31
41 cm	68.0	75.9	95.7	22.9	2.82	0.42	69.2	68.2	90.6	33.3	2.18	0.45
42 cm	56.5	84.5	96.7	19.6	3.64	0.51	55.4	77.3	91.5	28.1	2.44	0.58
43 cm	45.0	87.9	96.7	16.7	3.73	0.63	42.7	88.6	94.3	26.2	3.76	0.65
44 cm	36.6	94.8	98.3	15.8	7.07	0.67	31.3	95.5	96.8	23.9	6.88	0.72
≥ 45 cm	28.4	96.6	98.5	14.5	8.22	0.74	21.5	100.0	100.0	22.3	*	0.78
Neck circumference (AHI ≥ 30 events/h)												
38 cm	94.6	46.6	87.1	69.2	1.77	0.12	93.5	34.1	66.7	78.9	1.42	0.19
39 cm	92.3	60.3	89.9	67.3	2.33	0.13	90.3	40.9	68.3	75.0	1.53	0.24
40 cm	87.8	67.2	91.1	59.1	2.68	0.18	87.1	59.1	75.0	76.5	2.13	0.22
41 cm	78.7	75.9	92.6	48.4	3.26	0.28	77.4	68.2	77.4	68.2	2.43	0.33
42 cm	67.0	84.5	94.3	40.2	4.32	0.39	59.7	77.3	78.7	57.6	263	0.52
43 cm	57.0	87.9	94.7	34.9	4.72	0.49	54.8	88.6	87.2	58.2	4.83	0.51
44 cm	48.0	94.8	97.2	32.4	9.27	0.55	41.9	95.3	92.9	53.2	9.02	0.61
≥ 45 cm	38.9	96.6	97.7	293	11.29	0.63	29.0	100.0	100.0	50.0	*	0.71

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio; STOP-Bang: Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender (questionnaire); AHI: apnea-hypopnea index; pt(s): point(s); and SACS: Sleep Apnea Clinical Scale. *Not estimable.

predicting a diagnosis of OSAS—STOP-Bang score ≥ 5: 78.1% and 72.1%, respectively; SACS score ≥ 48: 54.9% and 84.1%, respectively; and an ANC ≥ 40 cm: 81.5% and 59.1%, respectively—as well as for predicting a diagnosis of severe OSAS—STOP-Bang score ≥ 5: 92.1% and 72.1%, respectively; SACS score ≥ 48: 66.1% and 84.1%, respectively; and an ANC ≥ 40 cm: 87.1% and 59.1%, respectively.

In the present study, the STOP-Bang questionnaire showed the best performance in a population at risk for OSAS, similar to what was reported in a study conducted in Brazil.[9] In a systematic review and meta-analysis, a STOP-Bang cutoff score ≥ 3 had an AUC of 0.72 (with a sensitivity and specificity of 90% and 49%, respectively) for predicting an AHI ≥ 5 events/h.[10] For predicting an AHI ≥ 30 events/h, the authors found the sensitivity and specificity of that same cut-off score to be 96% and 25%, respectively. However, when they applied a STOP-Bang cutoff score ≥ 5, the predictive performance of the questionnaire was similar to that found in the present study.

The SACS is easy to use, and a score of < 43 makes the presence of OSAS less likely. It can thus help clinicians exclude patients with very low probability of presenting OSAS. In addition, the simplicity of the index, which evaluates only four domains (daily functioning, social interactions, emotional functioning, and symptoms), makes it very attractive to use. A score ≥ 48 has a sensitivity and specificity of 72% and 84%, respectively, for the diagnosis of OSAS; therefore, patients meeting that criterion could be studied by HSAT.[2]

The ANC is the most useful anthropometric measure for the study of OSAS, more useful than weight and body mass index. Even when compared with nocturnal oximetry parameters, ANC has been shown to be better,[11] with an OR of 3.72 (CI: 2.2-6.31) when an ANC cut-off ≥ 41 cm is applied. In the present study, the ANC with the best sensitivity and specificity was 40 cm. This measurement is very useful in men who know their shirt size, because wearing a shirt with a ≥ 17-inch neck translates to having an ANC ≥ 43 cm, which has a sensitivity of 45% and a specificity of 88% for the diagnosis of OSAS.

Other questionnaires showed unclear utility in clinical practice. First, the Epworth Sleepiness Scale had the lowest sensitivity of the instruments used in predicting OSAS. Second, for the selected targets of ≥ 5 and ≥ 30 events/h, the snoring scale presented AUCs of 0.63 and 0.69, respectively. Another candidate, the Berlin questionnaire, was not tested, because of its documented poor performance in the Chilean population.[12]

In conclusion, among individuals suspected of having OSAS in Chile, the STOP-Bang questionnaire and the SACS, by virtue of their high sensitivity, may help clinicians identify those who do not require further study. In contrast, individuals with a STOP-Bang score ≥ 5, a SACS score ≥ 48, or an ANC ≥ 43 cm are likely to present OSAS, requiring prioritization of their diagnosis and treatment.

AUTHOR CONTRIBUTIONS

Dr. Jorge Jorquera (principal investigator): conception and design of the study, acquisition of data, data analysis, preparation of the manuscript, final revision, and technical support; Dr. Jorge Dreyse and Dr. Gonzalo Labarca: data analysis, critical analysis, manuscript correction, and final revision; Dr. Maria Ines Gaete and Constanza Salas: data analysis, critical analysis, manuscript correction, and final revision.

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Intraoperative support with venovenous extracorporeal membrane oxygenation for complex thoracic oncologic resection

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TO THE EDITOR:

When locally advanced lung carcinoma invades vital structures such as the heart, great vessels, and carina, it is often considered unresectable and therefore incurable. This is mainly due to the difficulty in the intraoperative management of the airways and intrathoracic vessels, given that, in some cases, conventional mechanical ventilation cannot maintain gas exchange.[1] In addition, in patients in whom the tumor is locally advanced, the surgical option can only be considered if resection is complete, with free surgical margins, that is, oncologically adequate.

Alternatively, the use of extracorporeal membrane oxygenation (ECMO)[2] can be the solution in such cases. ECMO is a method that can provide blood oxygenation, remove carbon dioxide, and ensure circulatory support when there is severe hemodynamic instability, as well as enabling protective/ultraprotective mechanical ventilation.[3]

We report two cases in which venovenous (VV) ECMO was used for intraoperative respiratory support for resection of lung tumors with proximal airway involvement, because conventional respiratory support was a limitation to surgery.

A 38-year-old woman presented with a 2-year history of exertional dyspnea. Chest CT (Figure 1A) showed a 4-cm heterogeneous solid lesion in the right lower paratracheal region, with signs of invasion of the right main bronchus (RMB) and medial extension to the carina and the origin of the (contralateral) left main bronchus. Bronchoscopy (Figure 1B) showed an exophytic infiltrating lesion causing subtotal obstruction of the RMB, and pathological examination revealed an adenoid cystic carcinoma with a low mitotic index infiltrating the airway wall. Because of the location of the lesion, we decided to perform carinal resection with right upper lobectomy and bronchoplasty with implantation of the bronchus intermedius into the residual carina with the assistance of VV ECMO. The patient was maintained in apnea during resection and anastomosis, and the endotracheal tube was retracted to allow for better visualization of the surgical field. After the procedure, the patient was decannulated from ECMO and extubated in the operating room and was referred to the ICU, where she remained for 2 days. The patient was discharged on postoperative (PO) day 5.

A 49-year-old male former smoker sought medical attention because of bronchopneumonia. During treatment, chest CT showed a right perihilar mass. A transthoracic biopsy revealed squamous cell carcinoma, positron emission tomography-CT (Figure 1C) confirmed the lesions, with no evidence of distant disease, and mediastinoscopy was negative. Because the lesion was centrally located, the proposed surgery consisted of right pneumonectomy with carinal resection and implantation of the left main bronchus into the trachea, since bronchoscopy (Figure 1D) revealed carinal involvement. For respiratory management, we decided to use VV ECMO and maintain apnea in both lungs with endotracheal tube retraction. During the operation, the tumor was found to invade the RMB, and we decided to perform a pneumonectomy, without the need for carinal resection. After surgery, the patient was decannulated from ECMO and extubated in the operating room. The patient was discharged from the ICU on PO day 2 and from the hospital on PO day 7 to outpatient adjuvant chemotherapy.

In both cases, VV ECMO was performed using the Seldinger technique, with an outflow cannula in the right common femoral vein and an inflow cannula in the right internal jugular vein (Figure 1E). The position of the cannulas was confirmed with transesophageal echocardiography during the operation. A centrifuge magnetic pump with a polymethylpentene oxygenation membrane (Rotaflow/Jostra Quadrox PLS; Maquet Cardiopulmonary AG, Hirrlinger, Germany) was used. Anticoagulation with heparin (1,000 UI) was used to achieve an activated clotting time of 180-200 s.

ECMO can be used in two configurations: VV and venoarterial (VA).[3] In VV ECMO, blood is drained from a vein, enters the ECMO circuit, and is returned through another vein. This configuration provides only respiratory support, providing blood oxygenation and carbon dioxide removal (Figure 1E). In complex surgical cases, VV ECMO allows adequate gas exchange independently of mechanical ventilation. In contrast, in VA ECMO, blood is drained from a vein, enters the ECMO circuit, and is returned through an artery, which combines cardiocirculatory support with the gas exchange function. In cases in which there is a risk of severe hemodynamic instability or in patients with pulmonary arterial hypertension, VA ECMO is an option for intraoperative management. VA ECMO can be performed via either the peripheral or central route, the latter by cannulating the heart base vessels, similarly to cardiopulmonary bypass (CPB).[1]

Intraoperative ECMO has proved useful also in cases of severe respiratory involvement, such as in patients who have previously undergone pneumonectomy and have an indication for resection of the remaining lung or in

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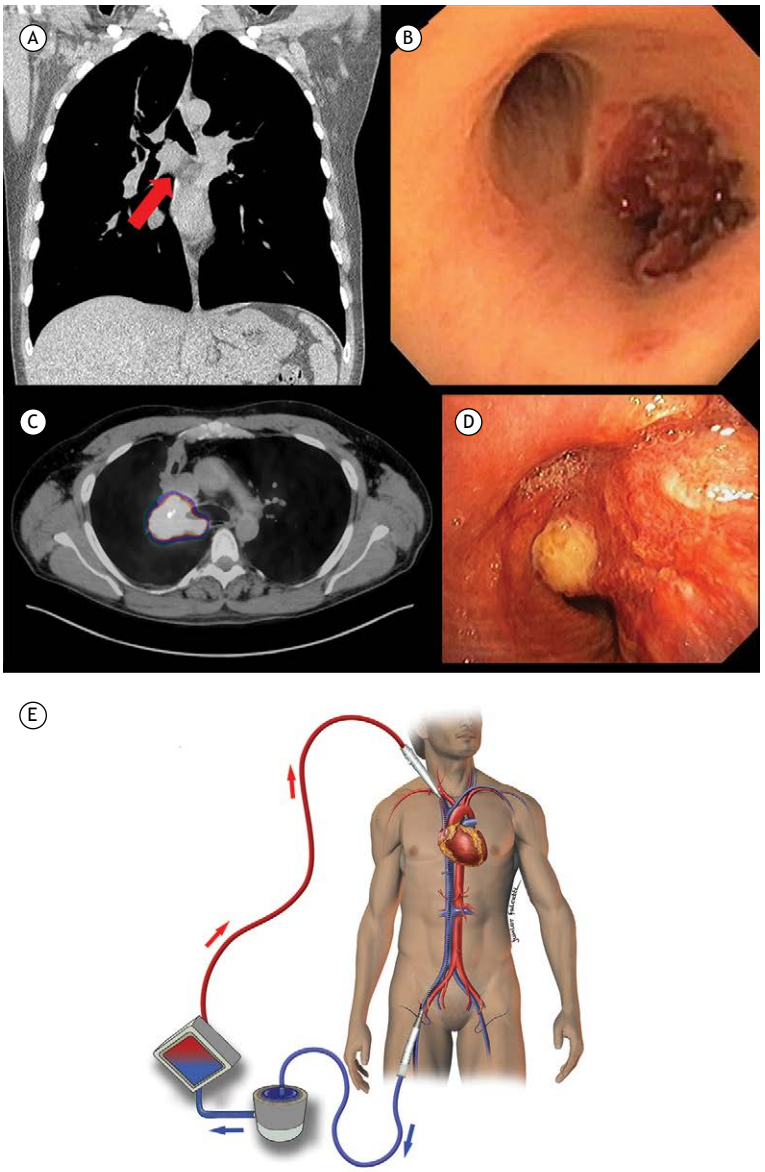

Figure 1. In A, chest CT showing a centrally located tumor with carinal involvement (arrow). In B, bronchoscopy showing the carina and tumor. In C, positron emission tomography of the chest showing a centrally located tumor with carinal involvement. In D, bronchoscopy showing the right main bronchus at the level of the carina and carinal involvement. In E, schematic illustration of venovenous extracorporeal membrane oxygenation with an outflow cannula in the right common femoral vein and an inflow cannula in the right internal jugular vein.

patients who cannot tolerate intraoperative one-lung ventilation because of lung disease, such as severe COPD or advanced interstitial lung disease with low DLCO.[4]

One of the advantages of intraoperative ECMO over CPB is that, because it is a heparin-coated closed circuit, lower doses of heparin are used or heparin could even be dispensed with if flows are greater than 3 L/min. [5] In addition, in peripheral ECMO, the fact that the cannulas are not within the surgical field facilitates the surgical procedure, because they are not in the surgeon's field of view.[6]

A possible alternative to ECMO is mini-CPB, which consists of a closed-circuit cardiocirculatory support system that results in a lower inflammatory response and requires a lower priming volume (volume of solution within the circuit) than does conventional CPB. However, the cannulas are not heparin coated such as those of ECMO, and, therefore, anticoagulation should be similar to that of conventional CPB; in addition, the oxygenation membrane lasts 6 h and can be used only during the operation.[7] Another use of ECMO in airway surgery has been described in complex therapeutic endoscopic procedures and in congenital stenosis in children.[8,9] Because children's airways are small, minimal edema can lead to airway impairment. The use of ECMO in the postoperative period makes it possible to maintain clinical stability until the edema

is reduced and bronchoscopy is performed, with no impairment of gas exchange.[10]

The most commonly described complications of ECMO are thrombosis, bleeding at the site of cannula insertion, blood flow limitation, and infection. However, these complications are related to the timing of ECMO initiation.[11]

Despite initial concern, there is no evidence of tumor dissemination due to the use of ECMO, just as there is no evidence of tumor dissemination due to the use of CPB.[1] Therefore, in extensive oncologic lung resection or in oncologic lung resection with severe involvement of central airways, VV ECMO, when available, has proved to be a safe option for ensuring patient oxygenation and ventilation, allowing airway manipulation and turning some complex cases that are difficult to resect into potentially curable cases.

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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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