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HIGHLIGHT

2021 SBPT recommendations for the management of severe asthma

Malîgnant pleural mesothelioma

Lung function of patients hospitalized with COVID-19 after hospital discharge

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

1 dia inteiro
de controle de sintomas[3,4]

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

Recomenda-se duas doses (jatos) em cada narina uma vez ao dia[6]

Referências: *Corticosteroide tópico nasal - 1. Meltzer EO. Ann Allergy Asthma Immunol 2007; 98: 12-21. - 2. Patel P et al. ENT J. 2008; 87: 340-353. - 3. Meltzer EO et al. Ann Allergy Asthma Immunol 2007; 98: 175-181. - 4. Ratner PH et al. J Allergy Clin Immunol 2006; 118: 1142-1148. - 5. Chervinsky P et al. Ann Allergy Asthma Immunol 2007; 99: 69-76. - 6. Bula do Produto Omnaris, Data de acesso das informações: 2019.

OMNARIS® (ciclesonida) 1.1618.0265 INDICAÇÕES: Omnaris® é indicado para o tratamento de sintomas de rinite alérgica intermitente ou persistente, incluindo congestão nasal, coriza, prurido e espirros. CONTRAINDICAÇÕES: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. ADVERTÊNCIAS E PRECAUÇÕES: Raramente podem ocorrer reações imediatas de hipersensibilidade ou dermatite de contato após a administração de corticosteroides intranasais. Os pacientes com reação de hipersensibilidade conhecida a outros preparados de corticosteroides devem tomar cuidado quando usarem spray nasal de ciclesonida, pois pode ocorrer reação cruzada com outros corticosteroides. Pacientes em tratamento com medicamentos supressores do sistema imune são mais suscetíveis a infecções do que os indivíduos sadios. Varicela e sarampo, por exemplo, podem ter um curso mais grave ou até mesmo fatal em crianças ou adultos usuários de corticosteroides. Em crianças ou adultos que não tenham tido estas doenças ou não tenham sido adequadamente imunizadas, deve-se tomar cuidado particular para evitar sua exposição. Em caso de exposição a varicela ou a sarampo, o paciente deve procurar orientação médica adequada para tratamento profilático. Os corticosteroides intranasais devem ser administrados com cuidado principalmente a pacientes com infecções por tuberculose ativa ou inativa do trato respiratório, com infecções fúngicas ou bacterianas, locais ou sistêmicas, com infecções virais ou parasitárias sistêmicas ou com *Herpes simplex* ocular devido ao potencial de piora dessas infecções. Efeitos nasais locais: Ocorreram casos raros de perfuração do septo nasal em pacientes que administraram ciclesonida pela via intranasal. Por causa do efeito inibitório dos corticosteroides sobre a cicatrização de ferimentos, pacientes que tenham tido recentes úlceras no septo nasal ou sofrido cirurgia nasal ou trauma nasal não devem usar um corticosteroide nasal até que tenha ocorrido a cicatrização. Em estudos clínicos com Omnaris®, foi raro o desenvolvimento de infecções localizadas por *Candida albicans* no nariz e na faringe. Quando tal infecção surge, ela pode exigir tratamento com terapia local apropriada e descontinuação de Omnaris®. Portanto, pacientes em tratamento com Omnaris® por vários meses ou por um período mais longo devem ser examinados periodicamente quanto à evidência de infecção por *Candida* ou outros sinais de efeitos adversos sobre a mucosa nasal. Efeitos sistêmicos: Doses de Omnaris® maiores que as recomendadas devem ser evitadas. Quando usados em doses excessivas, efeitos corticoides sistêmicos podem ocorrer, como hipercorticismo e supressão adrenal, retardo de crescimento em crianças e adolescentes, diminuição na densidade mineral dos ossos, catarata e glaucoma. Se tais alterações ocorrerem, a dose de Omnaris® deve ser descontinuada devagar, consistente com os procedimentos aceitos para a descontinuação de terapia corticoide oral. Gravidez e lactação: A experiência com corticosteroides orais desde a sua introdução demonstra que, pelo fato de haver um aumento natural na produção de corticosteroides durante a gestação, a maioria das mulheres precisará de uma dose exógena de corticosteroide menor. Muitas nem precisarão de tratamento com corticosteroides durante a gestação. Categoria C de Risco na Gravidez – não existem estudos clínicos bem controlados em gestantes. Tal como acontece com outros corticosteroides, a ciclesonida deve ser administrada durante a gravidez somente se o benefício potencial para a mãe justificar o risco potencial para a mãe, o feto ou o bebê. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Não se sabe se a ciclesonida é excretada no leite humano. Entretanto, outros corticosteroides são excretados no leite humano. Deve-se tomar cuidado se Omnaris® for administrado a lactantes. Omnaris® só deve ser administrado quando o benefício para a mãe que estiver amamentando for considerado maior que o risco potencial para a mãe e/ou criança. Efeitos não-teratogênicos: Pode ocorrer hipoadrenalismo em bebês nascidos de mães que tenham recebido corticosteroides durante a gestação. Pacientes pediátricos: Estudos clínicos controlados demonstraram que os corticosteroides intranasais podem causar redução na velocidade de crescimento de pacientes pediátricos. Os potenciais efeitos sobre o crescimento do tratamento prolongado devem ser ponderados com os benefícios clínicos obtidos e a disponibilidade de tratamentos seguros e efetivos alternativos aos corticosteroides. Pacientes idosos: Os estudos clínicos de Omnaris® não incluíram um número suficiente de indivíduos com 65 anos de idade ou mais para determinar se eles respondem de maneira diferente dos indivíduos mais jovens. Em geral, a seleção da dose para um paciente idoso deve ser cuidadosa, normalmente começando na extremidade inferior da faixa de dosagem, considerando a maior frequência de diminuição da função hepática, renal ou cardíaca e de doenças concomitantes ou aplicação de outras terapias. INTERAÇÕES MEDICAMENTOSAS: Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (*steady state*), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal. Não se verificaram interações de Omnaris® com a alimentação. POSOLOGIA: Para crianças acima de seis anos de idade e adultos recomendam-se duas doses (jatos) em cada narina uma vez ao dia (50 mcg por jato; total 200 mcg por dia). Não se devem aplicar mais de duas doses (jatos) em cada narina diariamente. Omnaris® deve ser administrado exclusivamente pela via intranasal. A dose máxima diária recomendada é de 200 mcg por dia. A duração do tratamento dependerá da resposta ao uso da medicação e deve ser estabelecida pelo médico. REAÇÕES ADVERSAS: As reações adversas mais comuns que podem ocorrer durante o uso prolongado de Omnaris® são dor de cabeça, sangramento no nariz e infecções das vias aéreas superiores. Reações comuns (> 1/100 e < 1/10): Respiratórias – sangramento do nariz (8,4%), irritação da mucosa do nariz (4,3%); Sistema nervoso – dor de cabeça (1,6%). Reações incomuns (> 1/1.000 e < 1/100): Gastrintestinais – boca seca (0,2%), dispepsia (0,2%); Infecções – candidíase (0,2%), rinite (0,2%); Respiratórias – ressecamento nasal (0,4%), dor na garganta (0,4%), secreção nasal (0,3%,), irritação na garganta (0,2%); Outras – transtorno do paladar (0,2%), aumento do número de leucócitos (0,3%). Reações com frequência não conhecida (frequência não pode ser estimada a partir dos dados disponíveis): Perfuração do septo nasal. VENDA SOB PRESCRIÇÃO MÉDICA.

Contraindicações: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. **Interações medicamentosas:** Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (steady state), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal.

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
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Office: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218. Website: www.sbpt.org.br. E-mail: sbpt@sbpt.org.br

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Severe asthma in Brazil: from diagnosis to treatment

Eduardo Vieira Ponte[1], Adelmir Souza-Machado[2]

Improved access to inhaled corticosteroids has contributed to an important reduction in asthma-related morbidity and mortality in Brazil and worldwide.[1,2] However, some individuals with asthma remain symptomatic despite having been prescribed adequate doses of inhaled maintenance therapy. For these patients, it is crucial to confirm that the asthma diagnosis is correct, as well as to identify and mitigate modifiable aggravating factors that contribute to the lack of asthma control, such as improper use of inhalers, poor treatment adherence, exposure to environmental stimuli, and uncontrolled comorbidities. After that, if asthma remains uncontrolled, a diagnosis of severe asthma can be established.[3]

Approximately 3.7% of asthma patients have severe disease.[4] Despite this relatively low prevalence, patients with severe asthma are particularly susceptible to loss of quality of life and lung function, as well as to exacerbations requiring hospitalization.[5,6] In addition to the unfavorable outcomes directly related to asthma, the use of high doses of inhaled medications and the frequent use of systemic corticosteroids in these patients, despite minimizing morbidity and mortality from respiratory events, add morbidity related to the systemic effects of these drugs.[7] Among the most relevant systemic effects are loss of bone mineral density, increased blood glucose, weight gain, immunosuppression, etc.

This worrisome scenario has given rise to research aimed at better understanding the determinants of severe asthma. Advances in knowledge of immunopathology and pathophysiology have allowed the development of new treatments,[8] and clinical trials have shown that drugs previously used for other respiratory diseases, such as long-acting antimuscarinic bronchodilators, are also effective for the treatment of severe asthma.[9] Inhaled corticosteroids associated with long-acting β_2 agonist bronchodilators are usually the main therapeutic regimen for patients with severe asthma, whereas the addition of other drugs or non-pharmacological therapies should be guided by the phenotypic characteristics of each patient.[10] As an example, some biologic drugs are indicated for severe eosinophilic asthma, whereas the anti-IgE antibody is indicated for atopic individuals with high IgE; azithromycin, despite less robust evidence, has been indicated to prevent asthma exacerbations; and bronchial thermoplasty is the last resort for patients who do not respond to or do not meet criteria for biologic drugs.

If, on the one hand, the diversity of therapeutic options and the concept of precision therapy contribute to improving the prognosis of severe asthma, on the other hand, they make the management of this disease a little more complex. Therefore, severe asthma should be managed by specialists. However, it is not feasible that all patients with this condition are referred to centers of excellence that are usually affiliated with medical schools or with tertiary care centers in medium-sized and large urban areas. It is necessary that health care professionals who treat respiratory diseases in the secondary care setting are also trained and have the necessary resources to identify and treat severe asthma. It is in this context that the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) has published the "2021 Brazilian Thoracic Association recommendations for the management of severe asthma".[11] This document was compiled by a panel of 17 pulmonologists with clinical and research experience in severe asthma. The text objectively and didactically addresses the most relevant and up-to-date topics on this subject, such as the criteria for diagnosing severe asthma; useful biomarkers for phenotyping; important aspects of the immunopathology of severe asthma, the understanding of which is necessary to comprehend the rationale for using phenotype-guided management strategies; and the therapeutic options available in Brazil. When discussing the available therapies, the SBPT document[11] not only presents efficacy and safety results from the most recent clinical trials, but also provides evidence from real-world pragmatic studies that are adequate to the Brazilian reality.

This document[11] has the great merit of facilitating the dissemination of the most up-to-date knowledge on the subject, but disseminating this knowledge is just one of the necessary steps for widespread diagnosis and treatment of severe asthma. Currently, there are structural limitations outside referral centers that can make it difficult to comply with the SBPT recommendations in the context of the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). For example, the large number of patients relative to the number of health care professionals who treat respiratory diseases limits the amount of time available for each patient's consultation, which can compromise the quality of assessment; patients treated in public health care services often have financial limitations to solve household environmental problems; simple ancillary tests, such as spirometry, are not always available in less-populated urban areas; and complex ancillary tests required for the diagnosis of severe asthma, despite having progressively become more accessible, are not yet widely available.[12] In addition, access to biologic drugs and bronchial thermoplasty, which are not

1. Faculdade de Medicina de Jundiaí, Jundiaí (SP) Brasil.
2. Universidade Federal da Bahia, Salvador (BA) Brasil.

effectively available via SUS, is difficult. Fortunately, the latest update of the Brazilian National Ministry of Health's clinical protocols and therapeutic guidelines for asthma[13] incorporates two biologic agents, namely omalizumab and mepolizumab, into the treatment regimen for severe asthma proposed by SUS, opening up the possibility that these drugs will be available in the not too distant future.

The first step in solving a problem is getting to know it. We will work so that the "2021 Brazilian Thoracic Association recommendations for the management of severe asthma"[11] will be widely disseminated to physicians in our specialty and to those in related specialties and that pertinent information will be available to primary health care professionals, their patients, and health care administrators.

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Pulmonology in the 21st century and the mark left by COVID-19

Marcelo Alcantara Holanda[1,2]

Two years have passed since the first case of COVID-19, a disease caused by infection with a new coronavirus known as SARS-CoV-2, was reported in the city of Wuhan, China. The numbers related to the biggest pandemic in the last 100 years speak for themselves: approximately 255 million reported cases; 5.25 million deaths, more than 615,000 of which occurred in Brazil (11.7% of the total deaths); and a contingent of people with sequelae that has yet to be properly studied. The emergence of viral variants makes it unclear whether this pandemic will be completely overcome. Fortunately, in an unprecedented feat, vaccines were developed relatively quickly and more than 8 billion doses of those vaccines have been administered. Of those, 314 million were administered in Brazil, despite the dissemination of denialist ideas and actions by the federal government, which has led to a lack of national coordination and to misinformation, as well as to the harmful, unnecessary politicization of the health crisis, to the detriment of the fight that is based on key elements such as science, efficient management, and cohesive social support.[1,2]

Within the first few months of 2020, it was found that 10-15% of COVID-19 patients who required hospitalization developed difficult-to-treat hypoxemic respiratory failure, many of those patients evolving to severe ARDS. That presented a huge challenge. There were no guidelines for noninvasive ventilation. There was justified fear that such strategies would result in massive contamination of health care professionals on the front lines. The term "early intubation" was widely used, and, unfortunately, early intubation was common. A study of a cohort of the first 250,000 hospitalizations for COVID-19 in Brazil showed an alarming 80% in-hospital mortality rate among intubated patients.[3]

Every crisis is also an opportunity. Given the specific characteristics of COVID-19, pulmonologists were called upon to respond to and take the lead in the fight against the pandemic. Our participation has taken place on several fronts, including patient care, knowledge dissemination/sharing, interfacing with other specialties, research, and innovation, as well as in government actions, crisis management and communication with the populace.[4]

Pulmonologists were called upon to participate in patient care in emergency rooms, emergency departments, ICUs, and other hospital wards, in all regions of Brazil. We took on the coordination of health care clinics, defining/organizing the protocols/procedures and writing/disseminating technical guidance documents, as well as helping define structures, equipment, and processes, from oxygen therapy to extracorporeal membrane oxygenation support, in cooperation with other specialists (intensivists, anesthesiologists, and internists), primary care physicians, physical therapists, nurses, and many others, including managers of the Brazilian Unified Health Care System and the Brazilian private health care system. We were aware of the fact that our numbers were insufficient to carry out that Herculean task. There is a lack of education and practical training in mechanical ventilation, in Brazil and in the world at large. Of the 4,671 current members of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), only 328 (7%) are on the SBPT Intensive Care Committee. That demanded the recruitment of health care professionals who were inexperienced in this field, which required pulmonologists with expertise in the area to supervise and to conduct continuing education activities or to coordinate telemedicine activities created amidst the collapse of a large part of the health care system (Figure 1).[5]

One highlight during this pandemic has been the continuous, profuse, and comprehensive generation of knowledge regarding COVID-19, together with the production of evidence to support protocols and to promote the optimization of outpatient and inpatient care. To date, 48 articles on COVID-19, focusing on subjects ranging from epidemiological aspects to patient rehabilitation, have been published in the Brazilian Journal of Pulmonology. The ecosystem of innovation in healthcare gained momentum with the participation of pulmonologists in interdisciplinary teams aimed at developing new devices and procedures that could mitigate the multiple waves of the pandemic. In the state of Ceará, Brazil, we developed, in a short period of time, a helmet interface that is safe and effective for administering CPAP without a ventilator. That interface was approved for sale and distribution nationwide by the Brazilian National Health Oversight Agency, reaching thousands of patients in 2021.[6,7]

In the absence of a national education and awareness program on the COVID-19 pandemic, several personalities in the field of pulmonology were responsible for bringing information to the population and combating fake news. Pulmonologists were often the voice of evidence-based medicine in the media. For example, Dr. Margareth Dalcolmo, President-elect of the SBPT (2022-2023), received the "Makes a Difference" award from the newspaper *O Globo*.[8] Among medical societies, the SBPT worked intensively with the Brazilian Medical Association, the Brazilian National Ministry of Health, international societies, and various representative bodies, innovating and creating new digital communication channels. Of note

1. Universidade Federal do Ceará – UFC – Fortaleza (CE) Brasil.
2. Escola de Saúde Pública do Ceará Paulo Marcelo Martins Rodrigues, Fortaleza (CE) Brasil.

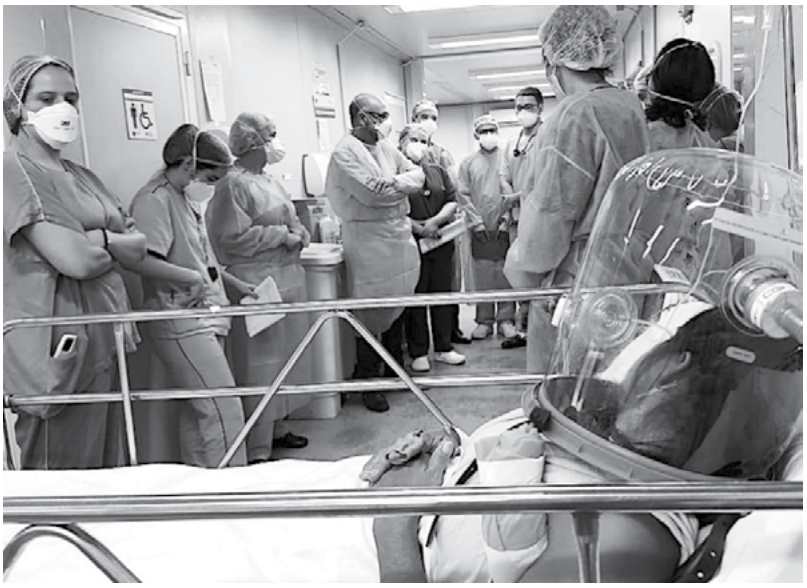

Figure 1. Photograph of a multidisciplinary visit at a respiratory clinic dedicated to COVID-19 patients at the Dr. Carlos Alberto Studart Gomes Messejana Hospital, in the city of Fortaleza, Brazil. In the foreground of the photograph, a patient receiving CPAP via a helmet interface watches a case discussion involving residents, physical therapists, nurses, and physicians from other specialties, performed under the supervision of the Department of Pulmonology.

is the performance of Drs. Irma de Godoy and Jaquelina Sonoe Ota Arakaki, who were the SBPT representatives on the COVID-19 Extraordinary Monitoring Committee. The Committee is a joint initiative of the Brazilian Medical Association and medical specialties; it works by consolidating information on the fight against the pandemic and by periodically providing quality guidance to citizens and health care professionals.[9]

It is certain that we will experience new catastrophes and pandemics in the future. The need to strengthen our specialty for the sake of health care systems is evident, and it is therefore necessary to expand training and continuing education for health care professionals. Our role in formulating and implementing public health policies in the field of respiratory medicine needs to be strengthened, from primary care and prevention of respiratory problems to advanced life support for critically ill patients requiring mechanical ventilation and rehabilitation. For us to evolve, such actions require valuing ethics, science, technology, and innovation, combined with humanist and social commitments as non-negotiable values of our profession and specialty. We are not the same as we were two years ago. We can be better.

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Less may be more: CPAP vs. APAP in the treatment of obstructive sleep apnea

Christiano Perin[1], Pedro Rodrigues Genta[2]

The most common first-line therapy for obstructive sleep apnea (OSA) is the use of positive airway pressure (PAP) devices during sleep. PAP directly relieves upper airway obstruction by increasing luminal pressure, thereby splinting the airway open. The use of PAP results in a clinically significant reduction in disease severity, sleepiness, blood pressure, and motor vehicle accidents, as well as improving sleep-related quality of life in adults with OSA.[1] PAP can be delivered by a fixed pressure (CPAP) during the entire sleep period or by auto-adjusting PAP (APAP) that varies the pressure according to obstructive respiratory events (airflow limitation or hypopnea/apnea) that are constantly detected by the device. Despite similar effectiveness and adherence, APAP is currently more often used than CPAP for long-term PAP treatment. In a study that assessed short-term PAP adherence in 2.62 million OSA patients, 50% of the devices were APAP devices, 41% were CPAP devices, and the remaining 9% were BiPAP devices or adaptive servo-ventilators.[2] The higher costs of APAP devices pose a special challenge to developing countries, including Brazil, where OSA is undertreated because of the lack of resources.

APAP is as effective as CPAP in terms of normalization of the apnea-hypopnea index (AHI) and improvement in sleepiness, quality of life, and neurocognitive function, with the advantage of significantly lower mean pressure applied during the night.[3] This could theoretically improve patient comfort with the device, therefore enhancing adherence. However, this is not supported by the literature. In a meta-analysis of 23 randomized controlled trials, no clinically significant difference was found between adults with OSA treated with APAP and those treated with CPAP in terms of average hours of use.[4]

As previously mentioned, a potential advantage of APAP over CPAP is the ability to automatically adjust therapeutic pressures as OSA severity changes with weight fluctuations, nighttime alcohol consumption, body position, sleep stages, and changes in upper airway anatomy. On the other hand, APAP has some disadvantages for some patients, including sleep disruption from pressure fluctuations[5] and the return of sleep-disordered breathing events when the PAP level is lowered by the device algorithms.[4] In addition, inappropriate or inadvertent increases in pressure can result in the development of treatment-emergent central sleep apnea or periodic breathing in certain patients.[6] Furthermore, in a randomized controlled trial comparing the impact of APAP with that of fixed CPAP on blood pressure in OSA patients, APAP did not reduce 24-h diastolic blood pressure as efficiently as did CPAP.[7] Other studies have found that APAP is not as effective as CPAP in reducing sympathetic tone during sleep[8] or in improving cardiovascular risk factors in OSA patients.[9] These findings might be due to microarousals caused by variations in therapeutic pressures during sleep and unintentional leakage caused by sudden increases in therapeutic pressure in response to respiratory events.[5] In one study,[10] patients on APAP were switched to CPAP if they were nonadherent, remained symptomatic, or complained of side effects. After switching from APAP to CPAP, patients showed improvement in adherence and sleepiness.[10] In comparison with those who were not switched to CPAP, those who were had more stage N1 sleep, a higher arousal index, and lower nadir oxygen saturation.[10] These results suggest that a subset of patients do better with CPAP than with APAP, possibly those with a lighter sleep and who are more prone to arousals during pressure adjustments by APAP devices.

In the current issue of the *Jornal Brasileiro de Pneumologia*, Alves et al.[11] present an interesting study carried out at a sleep medicine center in Portugal and evaluating the effectiveness and potential savings generated by the use of a protocol aimed at switching previously treated OSA patients from APAP to CPAP. They prospectively included 93 OSA patients who were well adapted to APAP therapy (i.e., who were adherent to treatment, had a normal AHI, and had no relevant air leak) to switch to fixed-pressure CPAP based on the 90-95th percentile of pressures recorded by the APAP device in the previous months. After an average follow-up of nearly two years, the authors found that only 5.4% of the patients did not tolerate switching to CPAP and had to return to APAP. Among those who tolerated CPAP, it was found that CPAP was as effective as APAP in controlling the AHI and improving sleepiness. Adherence to treatment was also similar, with CPAP having fewer adverse effects than APAP. Another striking finding was the estimated savings of more than €10,000 over the study period as a result of the use of PAP, given that the rental of CPAP equipment is cheaper than that of APAP equipment.

According to the authors,[11] the study has some limitations, including a possible selection bias, given that only patients who were well adapted and adherent to treatment with APAP were selected for CPAP therapy. Moreover, the fact that the study was carried out in only one center in Portugal can limit the external validity of the findings.

The findings of the study by Alves et al.[11] corroborate what we witness in daily practice, i.e., that most patients

1. LabSono, Hospital Mãe de Deus Center, Porto Alegre (RS) Brasil.
2. Laboratório do Sono, Laboratório de Investigação Médica 63, Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.

with OSA tolerate CPAP and APAP equally, with CPAP being better tolerated than APAP in some cases. Thus, CPAP may be the preferable option for a significant subset of patients.[10] What really increases adherence to PAP treatment is not the type of equipment, but educational initiatives and regular face-to-face and remote monitoring, allowing problem solving and positive reinforcement of the treatment.[12]

The study by Alves et al.[11] suggests that APAP should be used primarily as an initial therapeutic strategy for pressure titration. After a few days, switching to CPAP is as effective but cheaper. This strategy may be especially important in resource-poor settings such as Brazil. The savings generated by this approach could be used to provide therapy to a significantly larger number of patients.

CONFLICT OF INTEREST

None declared.

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The Sun also rises

Emanuel Sarinho[1], José Dirceu Ribeiro[2], Paulo Camargos[3]

Despite being present in minimal quantities, vitamins are essential for the proper functioning of the human organism. A healthy lifestyle and good dietary habits supply the minimum daily requirements, including that of vitamin D. Human beings have adapted over thousands of years to obtain vitamin D from natural sources, by synthesis in the skin from exposure in sunlight, or by consuming foods rich in its provitamin, such as eggs, cold-water fish, mushrooms, and cod liver oil.[1]

Adequate concentrations of vitamin D modulate the immune response and play a decisive role in respiratory health. In contrast, vitamin D deficiency (serum concentrations below 10 ng/mL) can result in inflammation of the airway smooth muscle, excessive mucus production, and bronchial hyperresponsiveness.

WHY DOES THAT HAPPEN?

Vitamin D is one of the lipophilic mediators that participate in innate and adaptive immunity. The activity of vitamin D is of greater importance for health in innate immunity, because it stimulates dendritic cells and innate lymphoid cells, as well as molecules such as cathelicidins and β-defensins, which have antimicrobial properties, promote immune/metabolic training, bolster epigenetic adaptation, and stimulate apoptosis. Vitamin D also favors the proliferation of tolerogenic dendritic cells and inhibitory receptors, thus protecting against unwanted inflammation. As for adaptive immunity, vitamin D helps minimize Th1/Th17 hyperfunction and modulate the Th2 response.[1,2] Vitamin D inhibits the Th2 response by stimulating production of the immunomodulatory cytokines TGF-β and IL-10. That production, together with stimulation of the Foxp3 transcription factor and regulatory T lymphocytes, blocks IL-13 and prevents exacerbation of Th2 inflammation. Likewise, B lymphocytes will predominantly produce IL-10 and IgG4 antibodies, thus blocking allergic phenomena. Therefore, vitamin D prevents eosinophilia and neutrophilia with excessive IL-8 production, inhibiting the proliferation and differentiation of plasma cells that secrete excess IgE, as well as the maturation of mast cells and their migration into the airways.[1,2]

HOW DOES THE WELL-ORCHESTRATED SET OF RESPONSES TO VITAMIN D TRANSLATE INTO CLINICAL PRACTICE?

In recent decades, there have been a number of studies evaluating vitamin D deficiency/insufficiency as a biomarker/risk factor in the prophylaxis and complementary treatment of asthma.[3] However, such studies, most of which were carried out in temperate countries with limited solar radiation throughout the year, have produced divergent results, as demonstrated in the conclusions of some systematic reviews and meta-analyses, such as one that included 36 studies evaluating serum vitamin D levels and complementary treatment of asthma with vitamin D versus placebo.[3] The authors of that systematic review and meta-analysis found that serum vitamin D levels were significantly lower among the children with asthma (n = 5,711) than among those without (n = 21,561). They also found that children who received vitamin D supplementation had fewer exacerbations than did those who received a placebo.[3] That finding is in keeping with those of other systematic reviews and meta-analyses, although such supplementation was not found to result in an improvement in lung function.[4,5]

One of the hypotheses raised to explain the lower number of exacerbations among individuals with asthma who receive vitamin D supplementation is that low levels of vitamin D predispose to viral infections, one of the main triggers of asthma exacerbations.[4] A comparison across studies indicates that there is statistical heterogeneity between clinical and functional outcomes. That could be attributed to several factors, including the serum vitamin D level at baseline, dose of vitamin D prescribed, and duration of supplementation; the age of the patients in the sample; latitude; sample variability; bias risk and control; follow-up time; and the use of medications, including oral corticosteroids, which are responsible for reducing serum vitamin D levels.[3-5] Another critical variable is inherent to the metabolism of vitamin D. It is known that vitamin D has a prolonged half-life and that daily supplementation for at least three months is necessary in order to reach a stable serum level. Therefore, different administration strategies and definitions of serum levels can generate different results.

The complexity of the relationship between vitamin D and asthma is amplified by the importance of variants in many genes that affect the regulation of vitamin D, which include the genes along the metabolic pathway, together with the genes of receptors in epithelial and bronchial smooth muscle, which increase the expression of various cytokines and interleukins, as well as contributing to the association between vitamin D and inflammation.[6]

A study published in this issue of the Brazilian Journal of Pulmonology sheds light on the whole range of comments, questions, and speculations regarding the relationship between asthma and vitamin D.[7] Despite the adoption

1. Área Acadêmica de Pediatria, Faculdade de Medicina, Universidade Federal de Pernambuco, Recife (PE) Brasil.
2. Departamento de Pediatria, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Campinas (SP) Brasil.
3. Departamento de Pediatria, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

of population-based sampling to obtain two comparable groups, that objective was not achieved for all of the study variables. For example, the statistically significant differences detected between age groups and school types, as well as the borderline difference in physical activity, could have introduced selection biases for both the prevalence of asthma and the serum levels of vitamin D. As pointed out by the authors, causal relationships cannot be established from cross-sectional studies; only cohort or case-control studies could provide an answer. In addition, it would be desirable to confirm the clinical diagnosis of active asthma through pulmonary function tests. However, the scarcity of studies of the issue carried out in tropical regions adds merit to the study conducted by Amaral et al.[7]

In the reality of clinical practice in Brazil and perhaps in its counterparts located in the tropics where, to paraphrase Ernest Hemingway, "the Sun also—and always—rises",[8] vitamin D deficiency/insufficiency is not the first diagnostic hypothesis raised when a clinician encounters a child or adolescent with uncontrolled asthma. In fact, a lack of asthma control is most often associated with failure to use or the inappropriate use of inhaled corticosteroids or other asthma medications, nonpharmacological measures, or comorbidity management. In the absence of a clinical response to such measures in children with low serum vitamin D levels, supplementation should be considered,[3] together with careful, systematic exposure to sunlight.[9]

Although there are many reasons for the rise of controversies around vitamin D, much of the blame can be laid at the feet of Dr. Michael Holick. Together with the discrepant findings published in scientific journals,[3-6] the subject has occupied editorial spaces in the lay press. According to an article published in The New York Times on 08/18/2018, Dr. Holick's enthusiasm for vitamin D surpassed the limits of good science practice and entered the nebulous terrain of conflicts of interest.[10] The artificial elevation of the reference values to levels higher than those previously considered the standard caused a pseudoepidemic of vitamin D deficiency and heated up sales of the supplement, as well as of diagnostic tests that generate financial gains of approximately US$1 billion a year.

We should always remember: the Sun also rises.

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Hypodensity at the lung base

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

A 22-year-old asymptomatic female patient underwent a chest computed tomography (CT) to clarify a hypertransparency in the left lung, seen on a chest X-ray. The CT scan revealed a hypodensity in the lower third of the left lung (Figure 1A), and CT angiography identified the presence of an anomalous vessel (Figure 1B).

Localized pulmonary hypodensities can be of a congenital or acquired nature. The leading causes of the acquired form are emphysema, hollow por cavitary, and air trapping (bronchiolitis, obstructive emphysema, Swier-James-McLeod syndrome). When analyzing the lesion, it is important to assess for the presence of walls, their thickness, and the existence of previous tests for comparison.[1]

Among the congenital conditions, bronchial atresia, congenital lobar emphysema (congenital pulmonary hyperinflation), bronchogenic cysts, cystic adenomatoid malformation, and pulmonary sequestration should be discussed. Some imaging characteristics can differentiate these conditions. In bronchial atresia, the presence of a secretion-filled dilated bronchus (bronchocele) within the emphysematous area is the diagnostic key. Bronchogenic cysts usually have defined walls and may be filled with fluid or air. In congenital lobar emphysema, the vessels, even if less numerous and smaller in caliber, can be observed in the middle of the hypodense area. Cystic adenomatoid malformation is usually composed of a multicystic mass.[1]

Pulmonary sequestration corresponds to a portion of the lung separated from the rest of the normal parenchyma receiving blood supply through an anomalous systemic artery, usually a direct branch of the aorta. The imaging feature that substantiates the diagnosis is the identification of the anomalous artery, which in most cases is located in the posterior basal segment of one of the lower lobes. The lesion can be cystic, uni- or multiloculated, solid or mixed, and may present fluid levels. Sequestration can be intra- or extralobar. In the more common intralobar form, the sequestered portion is limited by the visceral pleura of the normal lung. On the other hand, in the extralobar form, the sequestered parenchyma has its own pleural envelope. In general, patients with pulmonary sequestration are asymptomatic, but they may also have recurrent respiratory infections, especially in the intralobar form. The extralobar form is often associated with other congenital malformations.[1,2]

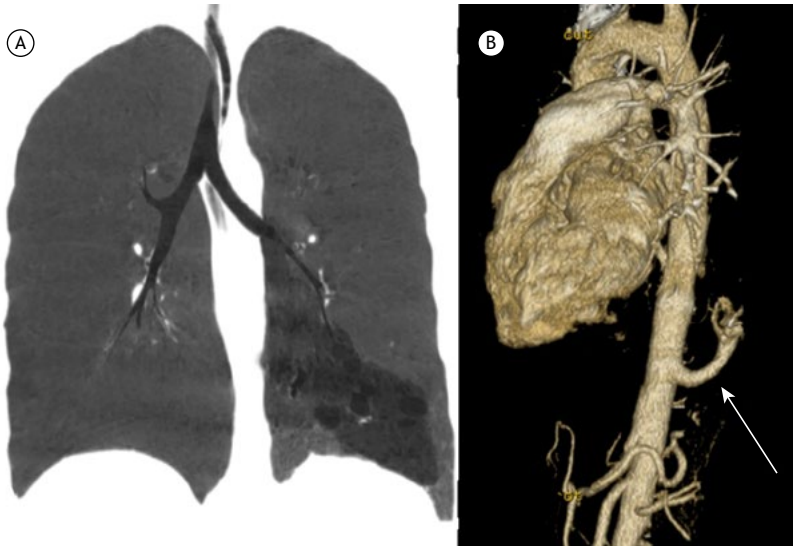

Figure 1. In A, computed tomography with coronal reconstruction in MINIP, evidencing a hypodense area in the lower third of the left lung lacking defined borders. In B, three-dimensional reconstruction showing the anomalous vessel emerging directly from the descending aorta (arrow).

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1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS), Brasil.

Building research capacity in Latin America and in Brazil: the MECOR program

Juliana Carvalho Ferreira[1,2], Irma de Godoy[3], Marcia Pizichinni[4], Ana Menezes[5], Cecilia María Patino[1,6]

WHAT IS MECOR?

The Methods in Epidemiologic, Clinical, and Operations Research (MECOR) is a training program created by the American Thoracic Society (ATS) to build clinical research capacity in low- and middle-income countries worldwide, with the purpose of improving respiratory health in these regions. The program started in Latin America in 1994 and now is offered in seven countries/regions around the globe. In Latin America, the program is a partnership among the ATS, the *Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Society), and four other respiratory societies: the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Society), the Mexican Thoracic Society, the Colombian Thoracic Society, and the Argentinean Thoracic Society.

The objective of the MECOR Program is to train investigators, academicians, clinicians, and public health practitioners to design and conduct rigorous and reproducible scientific research that is relevant to the needs of the settings in which they work.[1] Ultimately, the program serves the purpose to improve global lung health through the development of local, national, and regional research capacity.[1]

MECOR IN BRAZIL

The program is held in a Latin American country during one week every year. The first MECOR course in Brazil was in São Paulo in 1997. Since then, the course has been held in Brazil seven times, including the 2021 MECOR course, which was online due to the COVID-19 pandemic. In these 27 years, 621 Brazilian students have attended MECOR, comprising approximately 35% of the students overall (Figure 1). However, when the course is held in Brazil, approximately 60% of the students are from different regions in Brazil.

IMPACT

Given that MECOR is a research capacity building program, the expected impact is that Latin American graduates thrive as researchers in respiratory medicine, critical care, and sleep medicine and produce science that has regional relevance and improves lung health in Latin America. The challenge has been measuring such impact, a task that the strategic planning committee within the program has prioritized. Although we do not have objective indicators of long-term impact yet, many graduates have become leaders in respiratory medicine, critical care, and sleep medicine, as well as professors in Latin American universities and internationally recognized researchers. We highlight that, since 2012, both program directors and course leaders have been MECOR graduates, all faculty is from Latin America, most of them are program graduates, and all teaching assistants are graduates. This shows that MECOR produces scientists/educators who can maintain the level of excellence of the program. We highlight another important product of the MECOR program in Latin America: the continuing education series published in this Journal. The co-directors of the MECOR program have been contributing to the JBP with papers on scientific methodology since 2015, producing more than 30 manuscripts that have garnered hundreds of citations.

MECOR AND SBPT PARTNERSHIP

The mission of the MECOR program—to build research capacity in respiratory medicine—is aligned with the SBPT mission, which is to promote continuous professional growth and excellence and stimulate partnerships and scientific research.[2] Over these 27 years of MECOR in Latin America, the partnership has resulted in the participation of many SBPT members in the MECOR program, many of whom have become SBPT leaders. It has also strengthened the partnership between SBPT with ALAT and ATS in a coordinated effort to contribute to the development of future leaders in respiratory medicine in Brazil and Latin America.

WHY APPLY TO THE MECOR PROGRAM?

During their time in the MECOR program, students learn how to design and implement a research project that is relevant to their setting, and how to analyze, interpret, and communicate their findings in the form of a scientific manuscript.[3] The process is completed over three years, and students learn many research skills, in addition to basic biostatistics, critical appraisal of the literature, and presentation skills. Importantly, they network with colleagues from other regions and countries and become part of a community which feels like a family. This new community is very often a career and life changing experience.

1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Botucatu (SP) Brasil.
4. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina, Florianópolis (SC) Brasil.
5. Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas (RS) Brasil.
6. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles (CA) USA.

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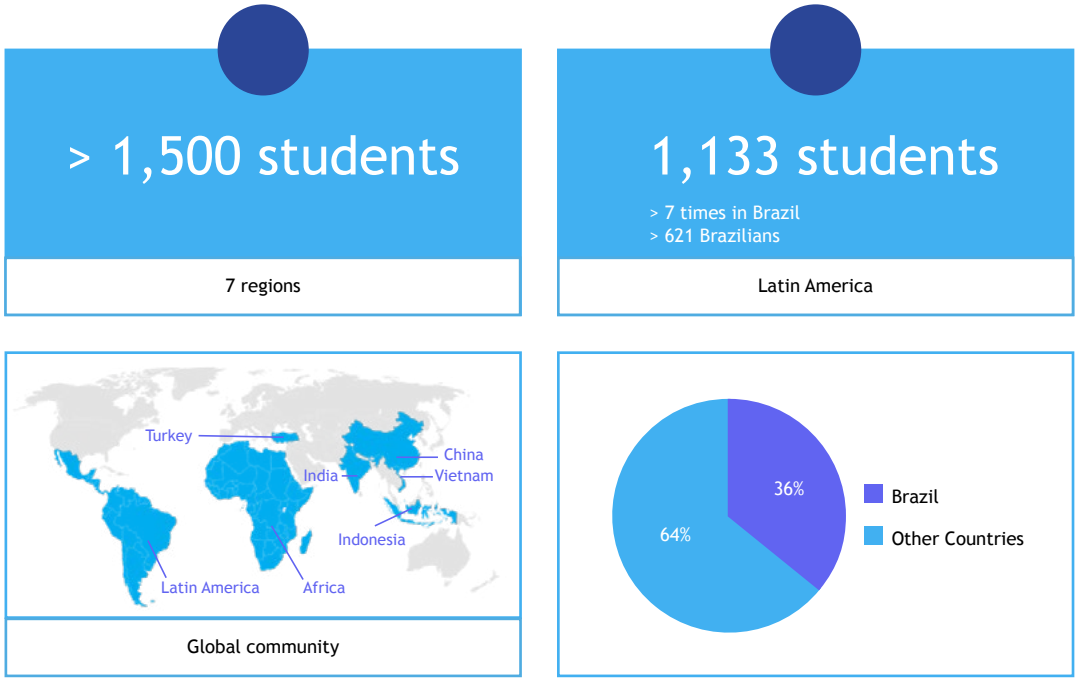

Figure 1. The MECOR program in Latin America and in Brazil.

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(Mis)Interpreting changes in pulmonary function tests over time

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

BACKGROUND

Pulmonary function tests (PFTs) are frequently repeated to judge whether potential changes, either spontaneously or after treatment, exceed test variability or surpass the effects of aging.[1] Although cutoffs for "significant" changes over time are available (Table 1), assessing their clinical relevance is substantially more complex. The reader should also consider the intervening effects of disease complications, comorbidities, thoracic surgery, and changes in body weight.

OVERVIEW

A 76-year-old man with mild interstitial pulmonary fibrosis ("patient A") but worsening dyspnea underwent PFTs 4 months after the last assessment. FVC and TLC decreased by ≈12%, raising concerns for disease progression. Alveolar volume (V_A), however, decreased in tandem with TLC (V_A/TLC remained ≈0.9). As DL_{CO} varied minimally (−3%), carbon monoxide transfer coefficient (K_{CO})—DL_{CO}/V_A—increased from 89% predicted to 148% predicted, indicating extraparenchymal restriction. Severe inspiratory muscle weakness was confirmed, and further investigations revealed motor neuron disease.[2]

A 10-year-old boy with cystic fibrosis ("patient B") showed recurrent, "significant" drops in FVC and, consequently, FEV_1 (up to 24%), indicating worsening gas trapping. After stabilization, both parameters markedly decreased again, leading the reader to suggest another exacerbation. Unbeknownst to him, however, the patient had developed bilateral transudative pleural effusions caused by hypoproteinemia and leading to decreased TLC.

A 55-year-old woman with severe asthma ("patient C") showed reduced FVC and FEV_1 over a one-year follow-up period. The results prompted changes in treatment, with deleterious consequences for dyspnea. Plethysmography revealed minor decreases in functional residual capacity (FRC) and RV, as well as a large reduction in TLC; of note, the BMI had increased from 38.7 kg/m^2 to 47.9 kg/m^2. Cardiopulmonary exercise testing revealed abnormalities consistent with morbid obesity.[3]

Assessing changes in PFTs is often more clinically valuable than making a single comparison with predicted values. The sources of confusion, however, are multiple.[4] For instance, it may arise when several parameters are followed, as some of them might indicate worsening just by chance (false positives). FEV_1 is arguably the most

Table 1. Suggested cutoffs for a "significant" decrease (i.e., changes above the measurement variability, changes associated with disease progression/worsening, or a combination of the two) in selected lung function parameters in adults.

Clinical scenario	FVC	FEV_1	DL_{CO}
"Normal" lung function			
Short-term	≥ 12% from baseline and 200 mL	≥ 12% from baseline and 200 mL	> 4 mL/min/mmHg
Year-to-year	≥ 15% from baseline	≥ 10-15% from baseline > 30-40 mL/year	> 10% from baseline
COPD			
Short-term	≥ 20% from baseline	≥ 20% from baseline	> 4 mL/min/mmHg or > 15% from baseline, whichever is greater
Year-to-year	Unknown	Unknown	Unknown
Asthma	≥ 12% from baseline and 200 mL	≥ 12% from baseline and 200 mL	Unknown
IPF and other progressive fibrosing ILDs	≥ 10% from baseline or a relative decline of ≥ 5 < 10% plus worsening respiratory symptoms, increasing fibrosis on chest imaging, or a combination of the two	Unknown	> 15% from baseline
Pulmonary hypertension	Unknown	Unknown	> 4 mL/min/mmHg or > 15% from baseline, whichever is greater

IPF: idiopathic pulmonary fibrosis; and ILD: interstitial lung disease.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, Kingston Health Science Center & Queen's University, Kingston (ON) Canada.
2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

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reliable parameter because it decreases in obstructive and restrictive diseases. However, it may decrease in a patient with obstructive disease because of the effects of incident restriction ("patient B"), and vice-versa. Moreover, wide fluctuations in FEV_1 over time are characteristic of asthma. Clinically relevant reductions in lung volumes and gas exchange efficiency[5] might be missed by FEV_1 alone. Establishing whether the rate of decline in FEV_1 in COPD is accelerated or not is even more challenging because of highly variable rates. Among lung volumes, FRC is the least variable over time (± 10%), but it is exquisitely sensitive to increases in BMI ("patient C").

CLINICAL MESSAGE

Discriminating between statistical significance and clinical significance is key to a cogent interpretation of longitudinal PFTs. If a change in a reproducible parameter (such as FEV_1 or FVC) is above the threshold of natural variability (Table 1), its practical relevance should be judged in light of clinical information. "Nonsignificant" decreases may sum up across sequential tests, leading to relevant decrements that are better appreciated when discrete values are plotted against time. In most circumstances, it is more likely that an actual change has occurred when it is demonstrated in more than two sequential measurements.

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ORIGINAL ARTICLE

Asthma and vitamin D in Brazilian adolescents: Study of Cardiovascular Risks in Adolescents (ERICA)

Cláudia Soïdo Falcão do Amaral[1], Érica Azevedo de Oliveira Costa Jordão[1], Cecília Lacroix de Oliveira[2], Mara Morelo Rocha Felix[3], Maria Cristina Caetano Kuschnir[1,4], Fábio Chigres Kuschnir[1,5]

1. Programa de Pós-Graduação em Ciências Médicas, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
2. Departamento de Nutrição Aplicada, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
3. Escola de Medicina e Cirurgia, Universidade Federal do Estado do Rio de Janeiro – UNIRIO – Rio de Janeiro (RJ) Brasil.
4. Núcleo de Estudos da Saúde do Adolescente, Universidade do Estado do Rio de Janeiro – NESA/UERJ – Rio de Janeiro (RJ) Brasil.
5. Departamento de Pediatria, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.

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Study carried out at the Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: To evaluate the association between asthma prevalence and serum levels of vitamin D in Brazilian adolescents. **Methods:** This was a cross-sectional, school-based study involving adolescents between 12-17 years of age from four large Brazilian cities located at different latitudes (Fortaleza, Rio de Janeiro, Brasília, and Porto Alegre). Information on asthma diagnosis, lifestyle, and sociodemographic characteristics was collected by means of self-administered questionnaires. Serum concentrations of calcifediol were dichotomized as sufficient (≥ 20 ng/mL) or insufficient/deficient (< 20 ng/mL) levels. Bivariate analyses were carried out between vitamin D levels and prevalence of active asthma (AA), as well as other variables in study, using the chi-square test. Generalized linear models were configured to analyze potential confounding factors ($p < 0.20$). **Results:** Between 2013 and 2014, 1,053 adolescents were evaluated. The prevalences of AA and insufficient/deficient levels of calcifediol were 15.4% and 21%, respectively. There were no statistically significant associations between AA and hypovitaminosis D. The prevalences of AA and vitamin D insufficiency were, respectively, 2.34 (95% CI, 1,28-4.30) and 3.22 (95% CI, 1.75-5.95) times higher in Porto Alegre than in Rio de Janeiro, regardless of possible confounding factors. However, no significant associations were found between the prevalence of AA and vitamin-D-related variables in any of the cities. **Conclusions:** No association was found between AA and low levels of vitamin D in adolescents living at different latitudes in Brazil.

Keywords: Adolescent; Asthma/epidemiology; Vitamin D.

INTRODUCTION

Asthma is a heterogeneous disease with several clinical phenotypes, being characterized by chronic inflammation of the lower airways. It is a global health problem with an increasing prevalence in recent decades.[1] According to the International Study of Asthma and Allergies in Childhood (ISAAC), the mean prevalence of asthma in Brazil in 2006 was 24.3% and 19.0% in children between 6 and 7 years of age and in adolescents, respectively, causing a significant burden on the health care system and the quality of life of patients and their families.[2] More recently, the *Estudo de Riscos Cardiovasculares em Adolescentes* (ERICA, Study of Cardiovascular Risks in Adolescents) revealed a prevalence of asthma of 13.1% in adolescents.[3]

The relationship between micronutrient deficiency and the etiology of asthma has been a subject of study in recent years.[4] Several studies have shown that vitamin D also participates in the pathogenesis of chronic, infectious, and autoimmune diseases.[5-7] There is an increasing number of studies pointing to a protective role of vitamin D and correlating its circulating levels with the severity and control of asthma.[5,6] However, the lack of consensus does not allow the general recommendation of using vitamin D as a supplement in asthma patients.[8,9]

Vitamin D deficiency is also considered a global public health problem, and its increased prevalence is closely related to changes in lifestyle, such as lack of exposure to sunlight, reduced intake of food sources of vitamin D, overweight/obesity, more indoor activities, and daily use of sunscreen. Low serum levels of vitamin D have been suggested to have a negative influence on lung function, number of exacerbations, and response to inhaled corticosteroids.[5,10,11] The aim of this study was to assess the association between asthma and serum vitamin D levels in adolescents in Brazil. Our hypothesis was that asthma might be more prevalent in adolescents with insufficient levels of this micronutrient.

METHODS

This study was an integral part of the ERICA project, a multicenter cross-sectional school-based study. The main objective of the ERICA was to estimate the prevalence of metabolic syndrome and cardiovascular risk factors in adolescents between 12 and 17 years of age, regardless of the sex, attending public or private schools in Brazilian

Correspondence to:
Cláudia Soïdo Falcão do Amaral. Rua São Francisco Xavier, 524, Maracanã, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 2868-8294. E-mail: claudiasfamaral@gmail.com
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cities with more than 100,000 inhabitants.[12] The study population was stratified into 32 geographical strata (27 capitals, including the Federal District of Brasília, and 5 sets with other municipalities in each macroregion of the country). A sample of 1,251 schools in 124 Brazilian municipalities was selected with a probability proportional to the population size. In each of the selected schools three combinations of shifts and grades were selected; within each of these combinations, one classroom was selected. All eligible students in the selected classrooms were included in the study. The design sampling weights were calculated by the product of the reciprocals of the inclusion probabilities in each sampling stage and were later calibrated considering the projections of the numbers of adolescents enrolled in the schools located in the geographical strata by sex and age. A total of 74,589 adolescents were evaluated. The ERICA sample has proven to be nationally and regionally representative, as well as in relation to each capital involved. Details of the sampling process have been described elsewhere.[13]

The sample of the present study was composed by a subsample of students who attended morning classes in 4 cities located at different latitudes: Fortaleza, Rio de Janeiro, Porto Alegre, and Brasília. Serum 25-hydroxyvitamin D levels were assessed.[12,13] The cities were selected because of their location and because their biorepositories were active during the study period. The participants were selected using proportional random allocation to ensure a thorough distribution of sex, age, skin color, season at data collection, and estimated sunlight exposure.[14]

Data collection included information on sociodemographic characteristics, such as sex, age, skin color, type of school (public or private), physical activity, season at blood sampling, and latitude according to the location of each city. Anthropometric measurements were taken.[12] Data were collected through a self-administered electronic questionnaire. The participants fasted for 12 h, and blood samples were collected at school, stored at −80°C, and subsequently analyzed at the same laboratory.[12] Variables regarding asthma were extracted from the written standardized questionnaire of the International Study of Asthma and Allergies in Childhood asthma module for the 13-to 14-year-old age group. The questionnaire had previously been translated to Portuguese and validated for use in Brazil.[15]

Active asthma (AA) was defined as the occurrence of at least one asthma attack in the last 12 months.[3] The other variables were categorized as follows: age range (12-14 years and 15-17 years); self-reported skin color (white, black, brown, yellow, or indigenous)[16] and categorized as "White" or "non-White"; type of school (public or private), and screen time (< or ≥ 2 h/day). The period of data collection was categorized according to the seasons (fall, winter, spring, or summer). Nutritional status and physical activity were also evaluated.[14,17,18] Physical activity was assessed using an adapted version of the self-administered Physical Activity Checklist, previously validated for Brazilian adolescents.[17] Participants performing ≥ 300 min/week of physical activity were classified as physically active.[17] Anthropometric measurements were performed with participants placed in a standing position, barefoot, and wearing light clothing, by means of an electronic scale (model P200M; Líder, São Paulo, Brazil) with a capacity of up to 200 kg (precision, 50 g) and a portable stadiometer (Alturaexata, Minas Gerais, Brazil; precision, 0.1 cm).[12] To assess the nutritional status of the participants, the WHO reference curves were adopted, the BMI-for-age being used according to sex. Those with a score of $+1 > Z \geq -2$ were considered to be of normal weight, whereas those with an index of $+2 > Z \geq +1$ or $Z \geq +2$ were considered to be overweight or obese, respectively.[19-21]

Calcifediol or 25-hydroxyvitamin D_3—25(OH)D—is produced in the liver by the hydroxylation of vitamin D_3 (cholecalciferol) by the vitamin D enzyme 25-hydroxylase and is the most stable form of vitamin D, maintaining high levels of vitamin D that reflect both sunlight exposure and dietary intake. Because 25(OH)D has a long half-life of approximately 24 h, it is routinely used to assess vitamin D status,[22] and its levels were measured by chemiluminescence microparticle immunoassay using a LIAISON 5000 series analyzer (DiaSorin Inc., Stillwater, MN, USA) and the DiaSorin kit. The coefficient of variation in percentage of this test varies from 3% to 8%, and its precision is 0.92 (95% CI, 0.90-0.94).[14] For analysis purposes, serum 25(OH)D levels were stratified into insufficient/deficient (< 20 ng/mL) or sufficient (≥ 20 ng/mL), based on the criteria adopted by the Department of Bone and Mineral Metabolism of the Brazilian Society of Endocrinology and Metabolism in 2017.[23]

Vitamin D dietary intake was assessed using a food record of all the meals consumed in the previous 24 h, including portion sizes and preparation methods. The data were collected using a software designed specifically for the ERICA.[14,18,24] After converting each food item to weight (g), the corresponding nutritional composition of each food was obtained by standardized tables, and the total diet of each participant was calculated. An intake of at least 400 IU/day of vitamin D was considered adequate.[25]

Statistical analyses were performed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA), using the set of commands for analyzing survey data with a complex sample (survey). Considering the sample size and the high prevalence of asthma (> 10%), the associations between serum 25(OH)D levels, prevalence of AA, and other study variables were assessed by bivariate Poisson regression models, using prevalence ratio (PR) and respective 95% CI.[26] Then, generalized linear models with Poisson family distribution were set up to analyze associations between 25(OH)D levels adjusted for potential confounding factors in the bivariate analysis ($p < 0.20$). For comparison between

the means of continuous variables, ANOVA and the Student's t-test were used. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Institute of Studies in Public Health of the Federal University of Rio de Janeiro (Protocol no. 45/2008).

RESULTS

Between February of 2013 and November of 2014, 1,152 adolescents underwent serum 25(OH)D determinations in the selected cities. Those who did not answer the question about asthma were excluded, the final sample consisting of 1,053 participants (91.4%). The prevalence of asthma in the sample was 15.4%, and insufficient levels of vitamin D were detected in 21.4%. The sociodemographic characteristics of the sample are described in Table 1.

Table 2 shows the distribution of the prevalence of AA according to sociodemographic characteristics, serum 25(OH)D levels, and nutritional status. There was a significantly higher prevalence of AA among those between 15 and 17 years of age and studying at private schools. Rio de Janeiro had the lowest prevalence of asthma. There was no association between insufficient levels of 25(OH)D and asthma.

Table 3 shows the distribution of the variables related to vitamin D according to the cities studied. The city of Rio de Janeiro, when compared with the other cities, had the lowest prevalence of vitamin D insufficiency (< 20 ng/mL), the lowest level of inadequate vitamin D intake (< 400 IU/day), and the highest serum

Table 1. Sociodemographic characteristics of the sample.

Variable	n	%	95% CI
Active asthma			
Yes	162	15.4	13.2-17.5
No	891	84.6	82.4-86.8
Serum 25(OH)D level			
Sufficient	828	78.6	76.1-81.1
Insufficient	225	21.4	18.8-23.8
Sex			
Female	643	61.0	58.1-64.0
Male	410	39.0	35.9-41.8
Age bracket, years			
12-14	431	40.9	35.9-41.8
15-17	622	59.0	58.1-64.0
Skin color			
Non-white	564	54.1	51.1-57.1
White	478	45.8	42.8-48.9
Type of school			
Public	754	71.6	68.8-74.3
Private	299	28.4	25.1-34.4
Nutritional status			
Normal/low weight	761	72.5	68.8-74.3
Overweight/obese	288	27.4	25.1-34.4
Physical activity			
Active	517	52.3	49.2-55.4
Inactive	471	47.6	44.5-50.7
Season at blood sampling			
Spring	337	32.0	25.1-34.4
Summer	134	12.7	10.7-14.7
Fall	219	20.8	18.8-23.8
Winter	363	34.4	31.6-37.3
City (latitude)			
Fortaleza (03°43'02" S)	292	27.7	25.1-34.4
Brasilia (15°46'46" S)	241	22.8	20.3-25.4
Rio de Janeiro (22°54'23" S)	250	23.7	21.1-26.3
Porto Alegre (30°01'59" S)	270	25.6	22.9-28.2
Screen time, h/day			
≤ 2	375	37.7	34.7 - 40.7
> 2	619	62.2	59.2 - 65.2

25(OH)D: 25-hydroxyvitamin D_3.

Table 2. Prevalence of active asthma in relation to sociodemographic characteristics, nutritional status, and serum 25-hydroxyvitamin D_3 levels.

Variables	Active asthma[a]	No asthma[a]	PR	95% CI	p*
Serum 25(OH)D level					
Sufficient	83.2 (75.7-88.7)	83.1 (80.3-85.6)	0.99	0.66-1.50	0.98
Insufficient	16.8 (11.3-24.4)	16.9 (14.4-19.8)			
Sex					
Female	51.9 (44.1-59.7)	51.3 (50.1-52.4)	1.02	0.75-1.40	0.88
Male	48.1 (40.3-56.0)	48.7 (47.6-49.9)			
Age bracket, years					
12-14	41.9 (35.7-48.4)	50.7 (49.8-51.7)	1.37	1.05-1.78	0.021
15-17	58.1(51.6-64.3)	49.3 (51.6-64.4)			
Skin color					
Non-White	56.3 (47.1-65.0)	56.3 (54.8-57.8)	1.01	0.69-1.46	0.97
White	43.7 (35.0-52.9)	43.7 (42.2-45.2)			
Type of school					
Public	38.0 (27.9-49.3)	22.2 (15.9-30.1)	1.91	1.44-2.55	0.000
Private	62.0(50.7-72.1)	77.8 (69.9-84.1)			
Nutritional status					
Normal/low weight	70.6 (61.0-78.7)	72.9 (68.5-76.8)	1.09	0.74-1.60	0.66
Overweight/obese	29.4 (21.3-39.1)	27.1 (23.2-31.5)			
Physical activity					
Active	63.3 (54.8 -70.9)	53.7 (49.9-57.4)	1.38	0.98-1.94	0.063
Inactive	36.7 (29.1-.45.2)	46.3 (42.5-50.1)			
Screen time, h/day					
≤ 2	32.6 (24.6-41.7)	39.3 (35.6-43.0)	1.43	0.93-1.97	0.112
> 2	67.4 (58.3-75.4)	60.8 (57.0-64.4)			
Vitamin D Intake					
≥400 IU/day	3.2 (1.0-9.58)	5.4 (4.3-6.8)	1.35	0.99-1.06	0.19
< 400 IU/day	96.84 (90.4-99.0)	94.6 (93.2-95.7)			
City					
Porto Alegre	14.6 (11.2-19.0)	10.9 (10.4-11.5)	1.00		
Fortaleza	23.6 (18.6-29.4)	19.7 (18.9-20.5)	0.86	0.55-1.35	0.52
Brasília	35.6 (29.3-42.5)	20.8 (19.8-21.8)	1.24	0.80-1.93	0.33
Rio de Janeiro	26.2 (19.4-34.4)	48.6 (47.5-49.6)	0.41	0.24-0.72	0.002
Season at blood sampling					
Fall	14.3 (8.6 -22.8)	14.6 (9.2-22.4)	1.00		
Spring	37.5 (27.1-49.3)	38.9 (30.7-47.9)	1.02	0.64-1.62	0.949
Summer	20.1 (11.7-32.5)	18.8 (12.4-27.4)	0.95	0.52-1.74	0.87
Winter	28.1 (20.3-37.5)	27.7 (22.0-34.2)	0.97	0.61-1.55	0.90

25(OH)D: 25-hydroxyvitamin D_3; and PR: prevalence ratio. [a]Values expressed as % (95% CI). *Bivariate Poisson analysis.

25(OH)D levels, and such differences were statistically significant. Although vitamin D intake (μg/day) was also higher in Rio de Janeiro, this difference was not statistically significant when compared with the other cities. However, no significant associations were found between the prevalence of AA and vitamin D-related variables in any of the cities (data not shown).

When the total sample was analyzed, those with an intake < 400 IU/day had lower serum 25(OH)D levels than did those with an intake of ≥ 400 IU/day (ANOVA; $p < 0.001$) or those with vitamin D insufficiency (17.2% vs. 11.0%; PR = 1.18; 95% CI: 0.34-4.62). However, the latter association was not statistically significant.

The comparison between the participants in Porto Alegre and those in Rio de Janeiro regarding the prevalence of asthma and vitamin D-related variables remained significant regardless of adjustments for sex, age group, nutritional status, physical activity, and screen time (Table 4). In addition, the mean serum levels of 25(OH)D were significantly lower in Porto Alegre ($p < 0.0001$). However, vitamin D intake (μg/day) did not differ between the two cities ($p = 0.12$).

DISCUSSION

Despite the differences in the prevalence rates of asthma among the cities studied, no associations were

Table 3. Distribution of vitamin D-related variables according to the cities evaluated.

Variable	RJ	POA	FOR	BRA	PR	95% CI	p
VD insufficiency (< 20 ng), %	12.0	34.3	15.2	19.4	0.57	0.40-0.82	0.002*
VD intake (< 400 IU/day), %	93.3	96.3	95.6	96.7	0.97	0.94-0.99	0.041*
Mean serum VD level (ng/mL)	29.3	25.2	29.1	26.3			< 0.0001**
Mean VD intake (µg/day)	3.7	2.9	3.4	3.3			0.1869**

RJ: Rio de Janeiro; POA: Porto Alegre; FOR: Fortaleza; BRA: Brasília; PR: prevalence ratio; and VD: vitamin D. *Poisson regression comparing the prevalence of vitamin D insufficiency in RJ vs. other cities.**ANOVA.

Table 4. Comparison between Rio de Janeiro and Porto Alegre regarding the prevalence of active asthma and vitamin D-related variables.

Variable	PR	95% CI	p*	PRadj	95% CI	p**
Active asthma, %	2.24	1.42 - 3.52	0.001*	2.34	1.28 - 4.30	0.007
VD insufficiency (< 20 ng), %	2.90	1.87 - 4.48	0.000*	3.22	1.75 - 5.95	0.000
VD intake (< 400 IU/day), %	1.03	0.99 -1.08	0.126*	1.03	0.98 - 1.08	0.188

PR: prevalence ratio; PRadj: prevalence ratio adjusted for sex, age bracket, nutritional status, physical activity, and hours of screen time; and VD: vitamin D. *Bivariate Poisson analysis. **Poisson generalized linear models.

found between insufficient low levels of vitamin D and asthma in our sample.

A study carried out in the USA with adult patients demonstrated a positive correlation between serum vitamin D levels and lung function parameters (higher FEV_1 and FVC).[27] In the city of Viçosa, Brazil,[28] 124 patients in the 0-to 18-year age bracket were studied in order to correlate recurrent wheezing with serum vitamin D concentrations. There was an association between vitamin D deficiency and wheezing, and the authors raised the hypothesis that there is a greater susceptibility to acute respiratory tract infections with the onset of wheezing in the first year of life due to reduced serum levels of this vitamin and concluded that vitamin D supplementation was a protective factor for the studied population.[28]

Several studies have found evidence that vitamin D plays an important role in the pathogenesis of asthma by reducing airway inflammation through modulation of the immune system or improving the anti-inflammatory function of corticosteroids.[29-31]

Among the immunomodulatory properties of vitamin D, its action on innate immunity stands out: it reduces pro-inflammatory cytokines and increases autophagosomal and autophagic activity, as well as the adaptive immune response, characterized by the inhibition of T-cell proliferation (Th1, Th2, and Th17). Moreover, it reduces the expression of IL-2 and INF-γ, stimulates the suppression of cytotoxic T response, and increases the number of regulatory T cells, IL-10, and IgG4.[6,32,33] Clinically, a reduction in the incidence of infections, a better response to corticosteroids in asthma patients, and improvements in pulmonary function are observed, thus avoiding airway remodeling.[32] However, according to some authors,[34] the results of experimental studies that link specific dietary components to immunological changes and airway responses or inflammation rarely translate into consistent randomized controlled trials, and, so far, none has been recommended as a preventive or therapeutic agent for asthma.

A study carried out in 2017 and involving 289 children and adolescents (9-19 years) in the city of Lima, Peru, 137 of whom had asthma, raised the hypothesis that the free circulating form of vitamin D is biologically active and more associated with asthma and atopy than are total serum levels of vitamin D. The authors suggested that total serum levels of vitamin D might explain the contradictions in the results found in the literature.[35]

In our study, we adopted the new cutoff points for total serum levels of vitamin D recommended by the Brazilian Society of Endocrinology and Metabolism.[23] These current values started to be used after considerations of which serum levels truly reflected the greatest harm to health and, consequently, the real need for vitamin D supplementation. The current consensus is that vitamin D levels < 10 ng/mL present health risks and require supplementation. The previous criteria used in order to classify vitamin D insufficiency, deficiency, and sufficiency (< 20 ng/mL; ≥ 20 ≤ 29 ng/mL, and > 30 ng/mL, respectively) have been discussed by various medical societies due to the worldwide hypovitaminosis D "epidemic", regardless of the different sociodemographic and cultural characteristics of the studied populations.[23] However, there was no association between serum 25(OH)D levels and asthma in our sample, even when the old cutoff points were used (data not shown).

Exposure to sunlight is an important factor for the absorption of vitamin D. Brazil is a tropical country, of continental dimensions, and great heterogeneity of climate. Most of the country is located between the Equator and the Tropic of Capricorn, which makes it one of the largest countries in the world in terms of land with high exposure to solar radiation throughout the year.[36] Serum concentrations of 25(OH)D vary according to geographic region and latitude and are higher in countries located close to the Equator.[37]

Of the four cities studied, Fortaleza (latitude: 03°43'02" S) and Rio de Janeiro (latitude: 22°54'23" S) had the lowest prevalences of vitamin D insufficiency

and higher serum 25(OH)D levels. In contrast, the prevalences of hypovitaminosis D were higher in Porto Alegre (latitude: 30°01'59" S) and in Brasilia (latitude: 15°46'46" S) than in the other two cities, and it could be explained by the large differences in latitude among them.[14]

The seasons also affect serum concentrations of 25(OH)D. When blood collection is performed in winter, the chance of hypovitaminosis D is greater.[14] In the present study, fewer blood samples were collected during summer due to school holidays. There is little seasonal variation in temperature in Rio de Janeiro and Fortaleza, whereas the climate is dry and there is little variation in solar radiation throughout the year in Brasília.[38] In Porto Alegre, however, climatic seasons are more clearly defined. In any case, there was no statistically significant association between the season at blood sampling and the prevalence of AA in our sample.

Interestingly, we found that the city of Rio de Janeiro, when compared with the other cities, showed significant favorable differences regarding vitamin D-related variables and the prevalence of AA. However, these findings were independent of the association between asthma and vitamin D levels.

Exploratory analysis comparing the distribution of these variables showed that the prevalences of asthma and vitamin D insufficiency was significantly higher in Porto Alegre (in southern Brazil) than in Rio de Janeiro (on the southeastern coast of Brazil) regardless of possible confounding factors. In addition to geographic distance, these two cities have important differences in climate, dietary habits, and rate of exposure to solar radiation.

In our sample, the lowest serum level of 25(OH)D was found among adolescents with a vitamin D intake of < 400 IU/day, suggesting a positive relationship between vitamin D intake and serum levels. Foods such as salmon, tuna, and cod liver oil, which are rich in vitamin D, are not usually consumed by Brazilian adolescents, who, in general, have shown a decline in healthy eating habits and consuming more processed foods.[14,39] Among the cities participating in the study, Porto Alegre had the lowest mean intake of vitamin D in µg, the highest rate of vitamin D insufficiency, and a high prevalence of asthma. Although proper nutrition is essential, it does not seem to be the only requirement for achieving acceptable levels of this vitamin.[37,40]

Cultural habits, the use of sunscreen, skin color, and the seasons of the year are among the factors that affect the absorption of vitamin D.[40] Rio de Janeiro showed higher vitamin D sufficiency, higher vitamin D intake (≥ 400 IU/day), and significantly higher serum levels of 25(OH)D when compared with the other cities studied, as well as showing a lower prevalence of AA. However, no significant associations were found between the prevalence of AA and vitamin D-related variables in any of the cities.

Some limitations of the study design should be considered, such as the impossibility of inferring causality for the associations found. The absence of lung function measurements due to the sample size and logistical issues made it difficult to compare our results with those of other studies that evaluated the association between asthma and vitamin D deficiency. On the other hand, the use of standardized procedures and trained staff ensured the good quality of the data. Furthermore, the random selection of participants and the sample size had sufficient power to ensure the reliability of the results obtained. Finally, the inclusion of geographic areas at different latitudes allowed the analysis of a large number of important confounding variables related to the association studied (exposure to sunlight, different lifestyles, and diet).

In conclusion, no association was found between AA and low levels of vitamin D in adolescents living at different latitudes in Brazil. Further studies are needed to elucidate whether this nutrient has any effect on asthma in a country with one of the highest incidences of solar radiation in the world.

AUTHOR CONTRIBUTIONS

CSFA: study conception and design; interpretation of results; and writing of the manuscript. EAOCJ and MMRF: analysis and interpretation of results. CLO and MCCK: manuscript review and final review of the submitted version. FCK: study conception and design; analysis and interpretation of results; manuscript review and final approval of the submitted version.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Lung function of patients hospitalized with COVID-19 at 45 days after hospital discharge: first report of a prospective multicenter study in Brazil

Eliane Viana Mancuzo[1], Carolina Coimbra Marinho[1], George Luiz Lins Machado-Coelho[2], Aline Priscila Batista[2], Jacqueline Ferreira Oliveira[3], Bruno Horta Andrade[1], Álvaro Lucca Torres Brandão[1], Ana Sophia Mitre Leite[4], Pedro Chaves Ferreira[1], José Reinaldo Corrêa Roveda[1], Arnaldo Santos Leite[1], Valéria Maria Augusto[1]

1. Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
2. Universidade Federal de Ouro Preto – UFOP – Ouro Preto (MG) Brasil.
3. Hospital Eduardo de Menezes - Fundação Hospitalar de Minas Gerais – FHEMIG – Belo Horizonte (MG) Brasil.
4. Faculdade de Ciências Médicas de Minas Gerais – FCMMG – Belo Horizonte (MG) Brasil.

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Study carried out at the Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: Because SARS-CoV-2 infection can severely affect the lungs and persistent functional changes can occur after severe disease, we aimed to determine lung function parameters of COVID-19 patients at 45 days after hospital discharge and compare changes according to the severity of the disease. **Methods:** This was a prospective descriptive analytical multicenter study. The participants were allocated into three groups: ward admission (WA) group; ICU admission not on mechanical ventilation (ICU/MV–) group; and ICU admission on MV (ICU/MV+) group. Lung volumes, DL_{co}, MIP, MEP, and six-minute walk distance (6MWD) were measured 45 days after discharge. **Results:** The sample comprised 242 patients (mean age = 59.4 ± 14.8 years; 52.1% of males), and 232 (96%) had altered lung function. In the total cohort, restrictive disorder was observed in 96%, as well as reductions in DL_{co} (in 21.2% of the patients), FEV_1/FVC (in 39.7%), and PE_{max} (in 95.8%), with no differences between the groups. Comparing the groups, the ICU/MV+ group had reduced DL_{co} in 50% of the patients ($p < 0.001$) and a lower mean 6MWD % of the predicted value ($p = 0.013$). Oxygen desaturation in the six-minute walk test was observed in 32.3% of the cohort and was less frequent in the IE group. **Conclusions:** This is the first South American study involving severe COVID-19 survivors whose lung function was assessed 45 days after hospital discharge. Changes were frequent, especially in those on MV, which highlights the importance of lung function evaluation after severe COVID-19.

Keywords: COVID-19; Respiratory function tests; Pulmonary diffusing capacity; Virus disease; SARS-CoV-2.

INTRODUCTION

In March of 2020, the SARS-CoV-2 infection, a highly contagious viral respiratory disease first described in December of 2019 and later designated COVID-19, was declared a pandemic by the WHO. About 5% of cases require ICU admission, and 2.3% require mechanical ventilation (MV).[1] Similarly to SARS and Middle East respiratory syndrome, other coronavirus infections, COVID-19 can severely affect the lungs, and hypoxemic acute respiratory failure and death can occur.[2] In addition, histopathological studies of severe forms of the disease showed alveolar damage, causing progressive respiratory failure.[3]

One early study assessing the lung function of patients hospitalized for COVID-19 immediately after discharge found that impaired DL_{CO} was the most common change, followed by restrictive ventilatory disorder, both associated with disease severity.[4] A 3-month follow-up study including 39 patients with changes on CT in the acute phase of the disease found a 16% reduction in DL_{CO} and an 11% reduction in FVC.[5]

Reduced exercise capacity in the follow-up period after COVID-19 has been described. In a cohort of 225 patients who performed the six-minute walk test (6MWT) 2 months after disease onset, patients with moderate or severe disease had shorter walking distance (6MWD) when compared with those with mild disease.[6] Among 186 patients undergoing the 6MWT 30-90 days after the onset of symptoms of COVID-19, those with persistent dyspnea had a lower 6MWD in percentage of predicted values (%pred) than did those without dyspnea.[7]

Respiratory muscle strength after COVID-19 has been poorly described to date. In a study of SARS survivors during the 2003 epidemic, a reduction in MIP and MEP was observed in a significant proportion of patients at 12 months of follow-up.[8]

Correspondence to:
Valéria Maria Augusto. Rua Guianas, 56/201, Sion, CEP 30320-100, Belo Horizonte, MG, Brasil.
Tel.: 55 31 3409-9746. E-mail: vmapneumo@gmail.com
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Clinical and functional follow-up assessment may detect persistent lung dysfunction and guide strategies to improve the outcomes of hospitalized patients with COVID-19.[9] The objectives of the present study were to describe the lung function of patients hospitalized for confirmed SARS-CoV-2 infection and SARS at 45 days after hospital discharge, and to compare the results between groups according to the severity of the acute disease. The hypothesis was that patients who required MV would have worse performance at follow-up than would those who did not.

METHODS

This was a prospective descriptive analyitical multicenter study that evaluated for inclusion adult patients admitted to three public referral hospitals for COVID-19 in the city of Belo Horizonte, Minas Gerais, Brazil, with a confirmed diagnosis of COVID-19 (positive RT-PCR result from nasal or oropharyngeal swabs) and SARS between June 16 and November 11 of 2020. The Brazilian Ministry of Health definition of SARS was adopted[10]: a hospitalized individual with fever and cough or sore throat, associated with dyspnea, feeling of tightness in the chest, or SpO_2 < 95%. Patients with indication for palliative care were considered ineligible. Patients who were too weak to perform the tests and those who withdrew consent were not included in the analysis.

This study was approved by the *Comitê Nacional de Ética em Pesquisa* (CONEP, Brazilian national research ethics committee), protocol number 4.044.191. Consent of the local ethics committees of the three hospitals was obtained. All participants gave written informed consent.

Of a sample of 551 patients who were considered eligible, a total of 294 (53.4%) were initially included. However, 49 were lost to follow-up (9 died, 7 withdrew consent, and 33 failed to attend follow-up), and 3 were too weak to perform the tests. Therefore, the final sample comprised 242 patients (43.9%).

Patients were stratified into three groups: ward admission (WA) group; ICU admission not on MV (ICU/MV−) group; and ICU admission on MV (ICU/MV+) group.

Demographics, clinical manifestations, comorbidities, continuous medications, smoking, date of onset of respiratory symptoms, date of hospital admission, length of hospital stay, length of ICU stay, length of MV, and complications during hospitalization were recorded. Laboratory tests and chest imaging at admission were performed at the discretion of the attending clinicians. Arterial blood gases, complete blood workup, C-reactive protein (CRP), LDH, serum albumin, prothrombin time/international normalized ratio (INR), D-dimer, creatinine, ALT, and AST results were recorded when available. Gas exchange was evaluated by the PaO_2/FiO_2 ratio. The proportion of pulmonary impairment on CT scans was recorded as informed in the reports provided by the radiology services of the hospitals.

The major outcomes studied were lung function (spirometry, lung volumes, and DL_{CO}), exercise capacity (6MWD), and respiratory muscle strength (MIP and MEP).

In accordance with the study design, assessment for eligibility and inclusion took place within 24 h of admission, and follow-up assessment was scheduled for 45 days after admission, with a tolerance of ± 15 days. This planning considered an expected average duration of hospital stay of 15 days and a transmission period of up to 30 days after the onset of symptoms. The assessment of patients with prolonged hospital stays was scheduled and carried out as soon as possible after discharge.

In the follow-up visit, the presence of cough and dyspnea (in accordance with the modified Medical Research Council scale),[11] as well as vital data, weight, and height, were recorded. Lung function tests were performed in the Pulmonary Function Laboratory of the University Hospital of the Federal University of Minas Gerais. A Collins CPL system (Ferraris Respiratory, Louisville, CO, USA) was used for the determination of absolute lung volumes, spirometry parameters, and DL_{CO}, in accordance with international criteria.[12,13] The helium dilution method in a constant volume system was used in order to measure lung volumes. The following variables were studied: TLC, slow vital capacity (SVC), FVC, FEV_1, and FEV_1/FVC ratio. Measurements were reported as absolute values and %pred for the Brazilian population.[14,15] The single breath method was used for the determination of DL_{CO}, considering the values suggested by Guimarães et al.[16]

The 6MWT was performed in a 30-m corridor using a portable oximeter (Nonin Medical Inc., Plymouth, MN, USA) in accordance with international standards.[17] The following variables were recorded: SpO_2, HR, RR, Borg dyspnea scale score at the beginning and end of the test, HR in %pred in relation to the maximum HR in %pred for adults, HR at the end of 6MWT, HR 1 min after recovery time, and 6MWD. Oxygen desaturation ≥ 4% or a change in HR 1 min after recovery time < 12 bpm were considered altered results.[18] The 6MWD was expressed in absolute values and in %pred for the Brazilian population.[19]

MIP and MEP were measured with an analog manometer (Makil, Londrina, Brazil), as described by Laveneziana et al.[20] The maneuver was repeated five to eight times, respecting a 10% reproducibility. The highest value obtained was recorded. Predicted values were calculated in accordance with Neder et al.[21] The lower limit of normal (LLN) for each variable was calculated from prediction equations.[13]

Diagnosis of COVID-19, lung function measurements, and selection bias were considered possible sources of bias. Diagnosis was defined by the gold standard test RT-PCR; the equipment used was calibrated according

to the recommendations of the manufacturers, and clinical evaluation followed standardized questionnaires applied by trained personnel. Selection bias was minimized by the multicenter design.

Data analysis

Data were collected using the REDCap platform (Vanderbilt University, Nashville, TN, USA) and analyzed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as frequencies and proportions. Continuous variables with normal distribution were described as means and standard deviations, whereas those with non-normal distribution were described as medians and interquartile ranges. Predicted values and LLN were used as risk to categorize continuous variables. Proportions were compared using Pearson's chi-square or Fisher's exact tests. The Kruskal-Wallis test or ANOVA was used for those with measures of central tendency. To verify differences between the groups, post hoc multiple comparisons, using parametric Student's t-test or nonparametric Mann-Whitney U test, were carried out. Hypothesis testing was two-sided, and the level of significance was set at $p < 0{\cdot}05$.

RESULTS

The analysis included 242 patients discharged from hospital during the study period. The WA, ICU/MV− and ICU/MV+ groups comprised 141 (58.3%), 70 (28.9%), and 31 (12.8%) of the participants, respectively. The groups were homogeneous regarding age (59.4 ± 14.8 years), sex (52.1% were male), level of education, family income, self-reported skin color, marital status, and comorbidities (Table 1).

The majority of the participants (86.4%) had at least one comorbidity. Asthma and COPD occurred in 11.1% and in 7.2%, respectively, and 62 patients (26.1%) were smokers (Table 1). The most common symptoms on admission were dyspnea (in 80.2%) and cough (in 68.6%), which were more frequent in the ICU/MV− group. Anosmia, dysgeusia, and diarrhea were more frequent in the WA group (Table 2).

Table 1. Sociodemographic characteristics and pre-existing conditions in the sample studied.[a]

Variable	Total	Group			p
		WA	ICU/MV−	ICU/MV+	
	(N = 242)	(n = 141)	(n = 70)	(n = 31)	
Male	126 (52.1)	71 (50.4)	36 (51.4)	19 (61.3)	0.540
Age, years	59.4 ± 14.8	61.0 ± 14.3	57.8 ± 14.9	56.2 ± 16.4	0.146
Level of education, years of schooling[b]					
> 12	20 (8.9)	11 (8.3)	8 (12.1)	1 (3.7)	
9-12	102 (45.3)	64 (48.5)	28 (42.4)	10 (37.0)	0.444
< 9	103 (45.8)	57 (43.2)	30 (45.5)	16 (59.3)	
Family income, MW[b]					
> 3	36 (16.5)	17 (13.4)	16 (24.6)	3 (11.5)	0.107
≤ 3	182 (83.5)	110 (86.6)	49 (75.4)	23 (88.5)	
Self-reported skin color[b]					
White	63 (26.1)	39 (27.9)	17 (24.3)	7 (22.6)	
Brown	128 (53.1)	71 (50.7)	38 (54.3)	19 (61.3)	0.915
Black	50 (20.8)	30 (21.4)	15 (21.4)	5 (16.1)	
Marital status[b]					
Not married	108 (46.8)	68 (49.6)	31 (46.3)	9 (33.3)	0.299
Married	123 (53.2)	69 (50.4)	36 (53.7)	18 (66.7)	
Pre-existing conditions					
Comorbidities	209 (86.4)	122 (86.5)	61 (87.1)	26 (83.9)	0.904
Hypertension[c]	143 (68.8)	79 (65.3)	46 (75.4)	18 (69.2)	0.380
Obesity[c]	75 (38.7)	40 (34.8)	26 (46.4)	9 (39.1)	0.340
Diabetes mellitus[c]	71 (34.0)	38 (71.1)	23 (37.7)	10 (38.5)	0.593
Other CVD[c]	37 (17.8)	19 (15.7)	12 (19.7)	6 (23.1)	0.605
Asthma[c]	23 (11.1)	15 (12.4)	5 (8.2)	15 (12.4)	0.693
COPD[c]	15 (7.2)	10 (8.3)	3 (5.0)	2 (7.7)	0.724
Smoking[b]	62 (26.1)	40 (29.0)	15 (21.4)	7 (23.3)	0.470
Use of immunosuppressive medication[c,d]	11 (5.4)	6 (5.1)	3 (5.0)	2 (7.7)	0.860
Other[b,e]	108 (51,7)	66 (54,1)	28 (45,8)	14 (53,8)	0,563

WA: ward admission; ICU/MV−: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; MW: minimum wage; and CVD: cardiovascular disease. [a]Values expressed as n (%) or mean ± SD. [b]Missing data ≤ 10%. [c]Missing data = 11-20%. [d]Prednisone > 20 mg/day for more than two weeks; cyclosporine; cyclophosphamide; mycophenolate; rituximab; azathioprine; chemotherapy within the past 30 days. [e]Active solid organ or blood cancer, chronic kidney disease, solid organ or bone marrow transplant, and other comorbidities.

Complications during hospitalization were more frequent in the ICU/MV+ group. Acute kidney injury occurred in 14 (5.9%) of the patients, 7 of whom required hemodialysis. Vascular thrombosis occurred in 27 (11.4%), being more frequent in the ICU/MV+ group (Table 2). Duration of MV was 11.5 ± 10.8 days. Tracheostomy was performed in 20 patients (66.7%) in the ICU/MV+ group.

Regarding laboratory screening and severity scores at admission, inflammation and acute phase markers—CRP, LDH, serum albumin, total leukocytes, neutrophils, and D-dimer—showed the greatest changes in the two ICU groups. Mean PaO_2/FiO_2 was significantly higher in the WA group than in the ICU groups. In contrast, SOFA scores were higher in ICU patients.

At admission, CT was performed in 164 (67.8%) of the patients, and pulmonary involvement > 50% was identified in 53 (32.3%), more commonly among the ICU patients.

The length of hospital stay was longer in the most severely ill patients and in those undergoing MV (Table 2). The mean time to follow-up assessment was 60.1 ± 21.7 days (range: 31-152 days) after admission and 46.4 ± 22.5 days (range: 4-136 days) after discharge. Intervals were shorter in the ICU/MV+ group.

Table 2. Clinical and laboratory characteristics at hospital admission and during the acute phase of COVID-19.[a]

Variable	Total (N = 242)	Group WA (n = 141)	Group ICU/MV− (n = 70)	Group ICU/MV+ (n = 31)	p
Symptoms					
Time from symptom onset to hospitalization, days	7.8 ± 10.0	8.2 ± 12.4	7.3 ± 5.8	7.2 ± 3.9	0.785
Dyspnea	194 (80.2)	103 (73.0)*	64 (91.4)†‡	27 (87.1)*,‡	0.004
Cough (dry or productive)	166 (68.6)	90 (63.8)*	58 (82.9)†	18 (58.1)*	0.008
Fever	141 (58.5)	84 (59.6)	41 (59.4)	16 (51.6)	0.706
Myalgia	119 (49.2)	72 (51.1)	31 (44.3)	16 (51.6)	0.624
Alterations in taste	103 (42.6)	73 (51.8)*	26 (37.1)†	4 (12.9)‡	< 0.0001
Alterations in olfaction	94 (38.8)	64 (45.4)*	23 (32.9)*‡	7 (22.6)†,‡	0.029
Diarrhea	63 (26.0)	45 (31.9)*	16 (22.9)*	2 (6.5)†	0.011
Rhinorrhea	46 (19.0)	32 (22.7)	11 (15.7)	3 (9.7)	0.175
Sore throat	43 (17.8)	25 (17.7)	14 (20.0)	4 (12.9)	0.690
Abdominal pain	26 (10.7)	15 (10.6)	8 (11.4)	3 (9.7)	0.964
Complications during hospitalization					
Vascular thrombosis	27 (11.4)	11 (7.9)*	8 (11.8)*‡	8 (26.7)†‡	0.014
Acute kidney injury	14 (5.9)	1 (0.7)*	5 (7.4)†	8 (26.7)‡	< 0.0001
Antibiotic use	223 (94.1)	129 (92.8)	64 (94.1)	30 (100.0)	0.317
Laboratory tests					
PaO_2/FiO_2[b]	279.1 ± 122.3	322.7 ± 119.1*	227.81 ± 104.5†	203.7 ± 90.1†	< 0.0001
SOFA score within the first 24 h[b]	2.3 ± 2.1	1.6 ± 1.3*	2.3 ± 1.3†	5.6 ± 3.5‡	< 0.0001
Total leukocytes/mm^3[b]	8,367 ± 4,137	7,875± 3,893*	8,519 ± 4,138*‡	10,277 ± 4,752†‡	0.014
Lymphocytes/mm^3[b]	1,208 ± 815	1,275 ± 905	1,180 ± 720	970 ± 494	0.170
C-reactive protein, mg/L[b]	97.9 ± 74.3	80.3 ± 59.4*	117.1 ± 82.8†	134.1 ± 91.5†	< 0.0001
LDH, U/L[b]	384.2 ± 159.9	336.5 ± 109.4*	422.5 ± 157.3†	521.8 ± 245.5‡	< 0.0001
Creatinine, mg/dL[b]	0.9 ± 0.6	0.8 ± 0.4*	0.9 ± 0.4*	1.4 ± 1.4†	< 0.0001
AST, U/L[c]	45.0 [34.0-64.0]	43.0 [33.0-61.7]	46.0 [37.0-65.1]	37.0 [46.0-78.3]	0.131§
ALT, U/L[c]	35.0 [25.0-62.7]	34.0 [23.0-62.0]	36.5 [27.0-61.7]	30.0 [36.0-65.0]	0.249§
D-dimer, µg/mL[d]	1,000 [579-1,647]	945 [579-1,514]*	1,120 [551-1,667]*	1,566 [774-6,164]†	0.039§
Lung involvement on chest CT scan[c]					
< 50%	111 (67.7)	79 (79.0)*	24 (51.1)†	8 (47.1)†	0.001
≥ 50%	53 (32.3)	21 (21.0)*	23 (48.9)†	9 (52.9)†	
Time outcomes					
Length of hospital stay, days	13.7 ± 11.9	8.7 ± 4.4*	15.8 ± 9.6†	31.4 ± 19.5‡	< 0.0001
Length of ICU stay, days	9.6 ± 14.5	-	6.6 ± 12.6	16.4 ± 16.3	0.002
Interval between discharge and follow-up evaluation, days[b]	46.4 ± 22.5	48.8 ± 19.9	45.1 ± 26.7	38.7 ± 22.4	0.069

WA: ward admission; ICU/MV−: ICU admission not on mechanical ventilation; and ICU/MV+: ICU admission on mechanical ventilation. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Missing data ≤ 10%. [c]Missing data = 11-16%. [d]Missing data = 21%. *,†,‡Equal symbols indicate similar means (Student's t-test with post hoc analysis) medians (Mann-Whitney U test), or proportions (Pearson's chi-square test). §Nonparametric test.

A TLC below the LLN was the most frequent alteration in lung function, detected in 96.8% of the cohort. However, the mean TLC %pred was above 80% in 87.9%. Only the ICU/MV+ group had a mean TLC %pred below 80% (79.5%), which was significantly lower than in the other groups.

The FEV_1/FVC ratio was below the LLN in 39.7% of the study cohort, but no difference was detected between the groups. The ICU/MV+ group had lower SVC %pred and FVC %pred, as well as a higher frequency of SVC, FVC, and FEV_1 below the LLN.

DL_{CO} was below the LLN in 21% of the cohort, but in 50% of the patients in the ICU/MV+ group. DL_{CO} %pred was significantly lower in this group.

A MEP below the LLN was observed in 95.8% of the cohort. Accordingly, the mean MEP %pred was 53.5%. The MIP below the LLN was found in 59.3% of the patients in the ICU/MV+ group. The mean MIP %pred in this group was 72.1%.

The 6MWD was similar between the groups. However, the 6MWD %pred was significantly shorter in the ICU/MV+ group. Oxygen desaturation was observed in 32.3% of the cohort and was less frequent in the WA group (Table 3). Table 4 presents other variables studied.

DISCUSSION

To the best of our knowledge, this is the first study reporting lung function parameters in survivors of severe COVID-19 in South America. The main results of this prospective study of 242 patients followed up at 45 days after discharge showed that 96% of those had some change in lung function, and functional impairment was greater and more common in patients on MV. The changes were characterized mainly by restrictive disorder, reduced DL_{CO}, and reduced 6MWD in association with oxygen desaturation.

Information on persistent symptoms and late changes in lung function after COVID-19 is widely available.[1,22-26] In our results, the ICU/MV+ group had a higher frequency of cough, but not of dyspnea, at follow-up assessment. A dyspnea score ≥ 2 was present in 18% of the patients after discharge. Huang et al.[26] evaluated 1,773 patients 6 months after hospital discharge and reported that 26% of those had a dyspnea score > 1, with a higher risk in the groups that had required high-flow oxygen and MV.

Although most patients in the present cohort had some abnormality in lung function, the changes were mild. Restrictive ventilatory disorder was the most prevalent one. This is in agreement with studies that included patients with moderate to severe COVID-19.[2,4,22,23] All subjects in the ICU/MV+ group had reduced TLC 45 days after discharge, but restrictive disorder was mild (TLC %pred = 79.5 ± 15.6%). Huang et al.[2] reported altered TLC in 12.6% of 30 patients evaluated 30 days after discharge; however, only 17 had severe disease. Another study reported that 35% of patients with a history of ICU admission still had TLC < 80% 6 months after hospitalization.[27]

Lung involvement > 50% was present in 32% of those who underwent CT at admission. This proportion was higher in the ICU/MV+ group (52.9%). Autopsy studies showed different degrees of alveolar structure destruction and interstitial fibrotic changes in patients who died of COVID-19, suggesting that this could be the mechanism of restriction.[26] In addition, ventilator-induced lung injury is a well-described post-SARS sequel, which may impact lung function recovery after severe illness.[28]

Reduced DL_{CO} is the most frequently described change after COVID-19, either in mild or in severe forms.[26,29-31] Reduced DL_{CO} was observed in 21% of the patients in our cohort and in 50% of those in the ICU/MV+ group. Other studies have shown similar results. Smet et al.[23] reported reduced DL_{CO} in 21% of 220 patients at 10 weeks of follow-up. An association between reduced DL_{CO} and severe COVID-19 has been described.[1,26,31] Guler et al.[24] reported reduced DL_{CO} in severe COVID-19 patients after adjusting the analysis for age, sex, and BMI. It has been suggested that decreased DL_{CO} after COVID-19 is not secondary to residual interstitial lung or vascular abnormalities, but rather a consequence of reduced alveolar volume.[30,31] Others have argued that reduced DL_{CO} could be associated with small vessel abnormalities and microthrombus formation.[26]

Obstructive ventilatory disorder was observed in 40% of the present cohort, which could not be explained by the reported frequencies of asthma and COPD in the study population; it is important to consider that predicted values were calculated according to national recommendations.[14] Smokers represented 26% of the cohort, and the frequency of obstructive pattern was higher in smokers than in nonsmokers (42% vs. 23%; p = 0.008; data not shown). A 9-year follow-up study of COPD in Brazil showed that this disease can be underdiagnosed in up to 70% of cases.[32] This could explain the finding of obstruction in patients with previously undiagnosed smoking-related COPD. However, information on previous respiratory symptoms or worsening wheezing after COVID-19 was not collected. Finally, the study cohort was selected from two referral hospitals for respiratory diseases and one referral hospital for infectious diseases. This may have introduced a selection bias for respiratory disease.

Obstruction could also be explained by the emphysematous abnormalities present in areas showing the "vacuole" sign on baseline imaging, as well as in areas with no lung infiltration. The former finding can be explained by direct parenchymal destruction caused by the infection, and the latter, as a manifestation of ventilator-induced lung injury.[22]

Impairment of expiratory muscle strength was similar in all groups, but reduced inspiratory muscle strength was mainly observed in the ICU/MV+ group. This could be consequent to transient changes in mechanical properties of the chest wall and respiratory muscles after critical illness and be attributed to the post-intensive care syndrome, which is characterized

Table 3. Cough, dyspnea, BMI, lung function results, and six-minute walk test results 45 days after hospital discharge.

Variable	Total	Group			p
		WA	ICU/MV−	ICU/MV+	
	(N = 242)	(n = 141)	(n = 70)	(n = 31)	
Dyspnea[b]	126 (52.3)	71 (50.7)	39 (55.7)	16 (51.6)	0.789
Dyspnea, mMRC ≥ 2	74 (59.2)	40 (56.3)	23 (59)	11 (73.3)	0.477
Cough[b]	60 (25.0)	25 (18.0)*	21 (30.0)*†	14 (45.2)†	0.004
BMI	30.8 ± 6.9	30.6 ± 6.9	31.4 ± 6.5	30.2 ± 7.9	0.639
Spirometry[b]					
SVC, %pred	83.7 ± 15.7	86.4 ± 14.6*	82.1 ± 17.0*	74.9 ± 14.0†	0.001
SVC < LLN	80 (35.4)	33 (25.0)*	28 (42.4)†‡	19 (67.9)‡	< 0.0001
FVC, %pred	80.3 ± 15.1	82.7 ± 14.0*	79.0 ± 16.3*†	72.7 ± 14.8†	0.003
FVC < LLN	93 (40.6)	42 (31.1)*	30 (46.2)†	21 (72.4)‡	< 0.0001
FEV_1, %pred	78.2 ± 15.9	79.4 ± 16.1	77.8 ± 15.6	73.7 ± 14.7	0.192
FEV_1 < LLN	96 (41.9)	48 (35.6)*	29 (44.6)*†	19 (65.5)†	0.011
FEV_1/FVC, %pred	78.3 ± 8.9	77.0 ± 9.9*	79.3 ± 6.7*†	82.0 ± 6.6†	0.009
FEV_1/FVC < LLN	91 (39.7)	58 (43.0)	24 (36.9)	9 (31.0)	0.423
Lung volumes[b]					
TLC, %pred	87.9 ± 15.8	91.2 ± 14.9*	85.0 ± 16.2†c	79.5 ± 15.6‡	< 0.0001
TLC < LLN	211 (96.8)	123 (96.9)	63 (95.5)	25 (100.0)	0.546
RV, %pred	89.6 ± 27.2	90.9 ± 26.2	89.6 ± 29.4	83.4 ± 26.6	0.430
RV/TLC, %pred	36.7 ± 9.9	37.1 ± 9.8	36.4 ± 10.0	35.6 ± 9.9	0.720
DL_{CO}[c]					
DL_{CO}, %pred	100.8 ± 26.0	107.1 ± 23.3*	96.3 ± 27.0†	81.9 ± 25.7‡	< 0.0001
DL_{CO} < LLN	46 (21.2)	14 (11.1)*	19 (29.2)†	13 (50.0)†	< 0.0001
Respiratory muscle strength[c]					
MIP, %pred	86.7 ± 30.5	86.6 ± 30.6*	93.0 ± 28.7*	72.1 ± 30.2†	0.011
MIP < LLN	88 (40.9)	52 (41.9)*,b	20 (31.3)*	16 (59.3)†	0.043
MEP, %pred	53.6 ± 18.1	53.8 ± 18.0	54.7 ± 18.2	50.4 ± 18.8	0.579
MEP < LLN	204 (95.8)	119 (96.7)	59 (93.7)	26 (96.3)	0.604
Six-minute walk test[b]					
Distance, m	437.1 ± 111.7	439.1 ± 114.5	449.4 ± 104.3	396.3 ± 110.4	0.107
Distance, %pred	83.8 ± 20.1	84.7 ± 19.6*	86.2 ± 20.9*	73.2 ± 18.3†	0.013
Oxygen desaturation during the test ≥ 4%	75 (32.3)	33 (24.1)*	30 (44.1)†	12 (44.4)†	0.006

WA: ward admission; ICU/MV−: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; mMRC: modified Medical Research Council dyspnea scale; SVC: slow vital capacity; %pred: % of predicted values; and LLN: lower limit of normality. [a]Values expressed as n (%) or mean ± SD. [b]Missing data ≤ 10%. [c]Missing data = 11-12%. *,†,‡Equal symbols indicate similar means (Student's t-test with post hoc analysis) or proportions (Pearson's chi-square test).

by the presence of physical, cognitive, or mental impairment in patients undergoing prolonged ICU stay,[33] including those with COVID-19.[31,34] Another possible explanation for respiratory weakness could be the occurrence of interstitial lung disease after COVID-19, which we cannot confirm due to the lack of lung imaging exams concomitant with functional assessment.[35] MEP was low in almost all patients (95.8%), whereas only 40.9% had reduced MIP. This discrepancy should not be expected when evaluating respiratory muscle strength. Indeed, volitional assessment of muscle strength is dependent on patient cooperation and coordination with the examiner.[36] Thus, our finding may be subject to false-positive results due to inadequate performance of the technique, such as incomplete seal of the mouthpiece.

Mean 6MWD %pred was significantly lower in the ICU/MV+ group. Similar results were reported in cohorts that included patients who required MV.[6,33] In contrast, Daher et al.[25] found even lower values in a sample of patients not on MV. However, those patients met the criteria for severe COVID-19 and had a mean of 64 years of age, which can reduce exercise capacity.[25] Another study with COVID-19 patients (mean age = 46.7 years) reported a mean 6MWD of 562 ± 45.3 m, and only 30% of their sample had severe COVID-19.[2] The worse performance of the patients who required MV in the 6MWT may be a consequence of critical illness polyneuropathy.[37] In addition, this fact may be associated with fatigue, the most common manifestation of the post-COVID syndrome.[37] More than 50 manifestations of the disease have been described and have been tentatively referred to as "late COVID-19," "post-acute COVID-19," or "post-COVID-19 syndrome." Fatigue was the most common symptom in a meta-analysis of post-COVID-19 patients, and its similarities

Table 4. Clinical and laboratory characteristics at hospital admission and during the acute phase of COVID-19, as well as lung function and six-minute walk test results 45 days after hospital discharge.

Variable	Total	Group			p
		WA	ICU/MV −	ICU/MV +	
	(N = 242)	(n = 141)	(n = 70)	(N = 242)	
Laboratory tests					
Neutrophils/mm^{3b}	6,550 ± 3,695	6,056 ± 3,471*	6,717 ± 3,752*	8,441 ± 4,030†	0.005
Platelets, ×1,000/mm^{3b}	248 ± 93	248 ± 99	258 ± 86	225 ± 87	0.279
Bilirubin, mg/dL^{c}	0.5 ± 0.3	0.5 ± 0.3	0.6 ± 0.4	0.5 ± 0.2	0.234
INR^{b}	1.05 [1.0-1.11]	1.03 [1.0-1.09]*	1.06 [1.0-1.13]†	1.07 [1.02-1.14]†	0.011
Spirometry^{b}					
SVC, L	3.1 ± 0.9	3.1± 0.9	3.0 ± 0.8	3.0 ± 0.9	0.831
FVC, L	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 0.8	2.9 ± 0.9	0.921
FEV_1, L	2.3 ± 0.7	2.2 ± 0.7	2.3 ± 0.6	2.3 ± 0.6	0.782
Lung volumes^{b}					
TLC, L	4.8 ± 1.2	4.9 ± 1.2	4.7 ± 1.2	4.6 ± 1.2	0.435
RV, L	1.7 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	1.6 ± 0.6	0.323
DL_{CO}^{b}					
DL_{CO}, mL.min^{-1}.mmHg^{-1}	22.1 ± 7.4	22.9 ± 7.0	21.6 ± 8.3	19.4 ± 6.9	0.077
Respiratory muscle strength^{d}					
MIP, cmH_2O	78.7 ± 29.9	77.4 ± 30.3	85.0 ± 28.0	69.6 ± 30.0	0.061
MEP, cmH_2O	93.1 ± 34.6	93.0 ± 36.7	94.4 ± 32.7	90.9 ± 29.8	0.910
Six-minute walk test^{b}					
HRR_1, bpm	95.6 ± 16.8	95.7 ± 16.1	94.5 ± 19.2	97.6 ± 13.9	0.715
ΔFinal HR − HRR_1, bpm	17.2 ± 14.7	16.6 ± 13.5	19.5 ± 16.9	15.07 ± 15.21	0.309
HRmax, %	70.0 ± 12.1	70.2 ± 12.5	70.3 ± 10.8	68.5 ± 13.4	0.773
Final Borg ± 4	92 (39.7)	61 (44.5)	24 (35.5)	27 (25.9)	0.134

WA: ward admission; ICU/MV−: ICU admission not on mechanical ventilation; ICU/MV+: ICU admission on mechanical ventilation; INR: international normalized ratio; SVC: slow vital capacity; HRR_1: recovery HR in the first minute; HRmax: maximum HR achieved; and Final Borg: Borg dyspnea scale score at the end of the test. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Missing data ≤ 10%. [c]Missing data = 25%. [d]Missing data = 11-16%. *,†Equal symbols indicate similar means (Student's t-test with post hoc analysis) or medians (Mann-Whitney U test).

with the chronic fatigue syndrome/encephalomyelitis syndrome (CFS/EMS) were described.[38] CFS/EMS can be associated with viral infections, such as Epstein-Barr virus, cytomegalovirus, enterovirus, and herpesvirus. Thus, SARS-CoV-2 could also cause CFS/EMS.

The strengths of the present study are the number of participants (N = 242), the inclusion of patients at different levels of disease severity, the assessment of different aspects of lung function, and the multicenter design. However, there are some limitations. First, there is a lack of information on previous respiratory symptoms and lung function, particularly in smokers. The obstructive disorders were more common in smokers, suggesting that some of them could have previous undiagnosed disease. The lack of chest imaging exams at follow-up also limited the correlation of ventilatory disorders with morphological changes. Second, appropriate investigation of respiratory muscle weakness as a cause of MIP and MEP reduction shall include nonvolitional techniques, such as diaphragm ultrasound and measurement of transdiaphragmatic pressure, which were not available. Third, there were variations in the interval between hospital discharge and follow-up assessment. Patients admitted to the ICU remained hospitalized for a longer time (Table 3) and were possibly evaluated later. One could speculate that the results would have been skewed by the longer time interval between admission and follow-up. To verify this possibility, we compared the outcomes in two groups according to the time to follow-up assessment after discharge: ≤ 60 days and > 60 days. Since no associations with that time were found for any of the demographic, clinical, or outcome variables, this possibility was not confirmed.

In conclusion, we found a high frequency of lung function alterations in patients hospitalized for COVID-19 after a 45-day follow-up, especially in those who underwent MV. The major changes were restrictive disorder, reduced DL_{CO}, reduced muscle strength, reduced 6MWD, and oxygen desaturation. These findings highlight the importance of long-term follow-up assessment of lung function parameters in severe COVID-19 survivors.

AUTHOR CONTRIBUTIONS

EVM: study conception and design; data collection, analysis, and interpretation; drafting and revision of the manuscript; and approval of the final version. CCM and GLLMC: study conception and design; data collection and analysis; drafting and revision of the manuscript for important intellectual content; and approval of

the final version. ABP: study conception and design; statistical analysis and tables; and approval of the final version. JGFO, BHA, ALTB, ASML, PCF, and JRCR: data collection, analysis, and interpretation; revision of the manuscript; and approval of the final version. ASL: study conception and design; data collection, analysis, and interpretation; database organization; revision of the manuscript; and approval of the final version. VMA: study conception and design; data analysis and interpretation; revision of the manuscript for important intellectual content; approval of the final version; and guarantor of the article.

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ORIGINAL ARTICLE

Impact of social distancing in response to COVID-19 on hospitalizations for laryngitis, tracheitis, otitis media, and mastoiditis in children aged 0 to 9 years in Brazil

Clovisa Reck de Jesus[1], Aline Antônia Souto Rosa[1], Amanda da Silva Meneses[1], Angélica Conzati Agostini[1], Fernanda Bercht Merten[1], Sofia Moreira Ferrão[1], Luíza Costa Silveira Martins[1], Frederico Orlando Friedrich[1], Leonardo Araújo Pinto[1]

1. Centro Infantil, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS), Brasil

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ABSTRACT

Objective: The objective of this study is to evaluate the impact of social distancing resulting from COVID-19 in hospitalizations for infections of the upper airways (URTI), such as acute laryngitis, tracheitis, and otitis media in children aged 0 to 9 years in Brazil, considering that they share the same forms of transmission. **Methods:** Data on hospitalizations for acute airway changes and their complications in children <9 years old were obtained from the Database of the Brazilian Department of Public Health Informatics for the period 2015 to 2020. These data were also analyzed by macroregions of Brazil (North, Northeast, Southeast, South, and Midwest). The effect of the social distancing strategy on the increase of acute laryngitis, tracheitis, otitis media, and mastitis, as absolute and relative reductions, was calculated by analyzing the annual calculation of 2015-2019 vs 2020. **Results:** All the hospitalizations compared in the Unified Health System (SUS) for laryngitis and acute tracheitis and otitis media decreased, considering all states of Brazil. The largest reduction in hospitalization reduction was in the North, with -94% in 2015-2019 vs 2020 in cases of laryngitis and acute tracheitis, and in the Midwest, with - 85% in 2015-2019 vs 2020 in cases of otitis media. **Conclusion:** Hospitalizations for laryngitis, acute tracheitis, and acute otitis media in children <9 years old decreased between March and July 2020 in Brazil, when social distancing measures were adopted due to the COVID-19 pandemic.

Keywords: COVID-19; Laryngitis; Otitis media; Confinement; Children; Hospitalization.

INTRODUCTION

In March 2020, the World Health Organization (WHO) declared a pandemic caused by a new species of coronavirus, COVID-19 (coronavirus disease 2019). This outbreak of the disease began in late December 2019, when patients with viral pneumonia due to an unidentified microbial agent were reported in Wuhan, Hubei Province, China.[1] Because of this, the "UPDATE OF THE COVID-19 Strategy", a document produced by WHO, in which guidance is provided to countries according to the epidemiological change expected with the evolution of the current pandemic, was published. Therefore, health authorities had to modify and implement some measures to restrict distance and circulation at the population level, in order to reduce exposure and prevent transmission of the virus.[2]

Upper respiratory infections (URI) are commonly found in pediatric emergency care services, mainly because they are common pathologies in acute respiratory infections in children. They present transmissibility mainly through droplets dispersed through coughing and sneezing (such as an aerosol), or even through contact of regions of the body contaminated with the airways of healthy individuals, such as hands.[3] For this reason, it is important to compare the prevalence of these diseases in a period of isolation, since the dissemination of URI often occurs in schools, daycare centers, public transportation, and other public environments, which have been closed or restricted concerning distance recommendations.

Among the most common URIs, the acute viral larynx, also known as viral croup, stands out, which consists of an inflammation of the subglottic part of the larynx during respiratory virus infection. Affection is more common in infants and preschoolers, with a higher incidence at two years of age. Its evolution varies, starting with symptoms of runny nose, fever, and cough and progressing to mild

Correspondence to:
Clovisa Reck de Jesus. Centro Infantil, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Av. Ipiranga, 6690, CEP 90610-000, Porto Alegre, RS, Brasil.
Tel.: 55 51 3320-3000. E-mail: clovisareckj@gmail.com
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to severe obstruction and difficulty breathing. Airway persistence usually lasts 48 to 72 hours and regression occurs after five days.[3] Most cases occur in autumn and winter but can manifest during any season.[4]

Bacterial tracheitis, on the other hand, is less common, but affects soft tissues of the trachea,[5] and can also expand into subglottic structures of the larynx and upper bronchial tree.[6] The main infectious agents are bacteria.[7] Affection is more common in children during the first six years of life, with the winter and autumn period being the most prominent in cases, coinciding with seasonal viral epidemics[5,8] Symptoms include fever, stridor, cough, dyspnoea, odynophagia, or dysphagia and voice change.[9]

Another very common infection in childhood is acute otitis media (AOM), especially in the preschool period, between six months and three years of age,[10] characterized by ear pain, otorite, fever, nocturnal agitation, decreased food intake, and drowsiness.[11] It is an inflammatory process, which can be viral or bacterial and usually occurs due to a complication of upper respiratory infection (URI). The risk factors for such infection are exposure to smoke, use of bottles and pacifiers, supine position, and, mainly, care in the daycare center.[10]

Therefore, it is important to highlight that the period of the beginning of restrictive measures due to the COVID-19 pandemic in Brazil occurred in February 2020, just before the autumn of the southern hemisphere, and remained throughout the winter (from March to September), a period in which there is a higher incidence of the pathologies described above. In China, in the same period, studies showed a concomitant decrease in influenza, enterovirus, and pneumonia. Therefore, the implementation of infection control measures, including the use of masks, hand hygiene, and social distancing to prevent the spread of COVID-19, may have had a strong impact on reducing the spread of other infectious pathogens in pediatrics.[12-15] Therefore, the aim of this study is to evaluate the early impact of social distancing due to COVID-19 and hospitalizations for acute laryngitis, tracheitis, and media otitis in children aged 0 to 9 years in Brazil.

METHODS

The design used was an ecological study, in which data were obtained on hospitalizations for laryngitis and otitis from the database of the Department of Informatics of the Unified Health System (DATASUS)[16] which provides the diagnosis of hospitalization for the period 2015-2020 (month by month). DATASUS presents absolute numbers of hospitalizations from the public system, obtained following the International Classification of Diseases, version 10 (ICD-10). It considers the main diagnosis in hospitalization, being able to store information with universal coverage of the Brazilian population.[17] To access the data, the links "Health Information" (TABNET) - "Epidemiological and Morbidity" (Epidemiology and Morbidity) - "Hospital Morbidity" (Hospital Morbidity), "Morbidity List" (Morbidity List), respectively for the age group from 0 to 9 years, were used. These data were also analyzed by the macroregions of Brazil (North, Northeast, Southeast, South, and Midwest), due to variations in population density, climatic variation, and socioeconomic factors, considering the continental extension of the country. The months of January to June of each year were researched since it covers the typical discharge seasons in hospitalizations for laryngitis, acute tracheitis, and otitis media, and other disorders of the middle and mastoid process. To evaluate the reliability of the report, malignant neoplasm of bone and articular cartilage was used as a comparison, since social distance measurements are not expected to have a major impact on these conditions.

As this is a search for data on a platform available online, with data fed by the single health system, without personal identification of the patient, it was not necessary to analyze and approve the Research Ethics Committee. The tool, therefore, counts on the number of hospitalizations that can be stratified according to age and location.

To evaluate the effect of pandemic containment measures about the incidence of the aforementioned diseases, absolute reduction (without and with pandemic containment measures) and relative reduction (without and with pandemic containment measures) were calculated by analyzing the subsets 2015-2019 vs 2020. Thus, two analyses were made: the first aiming at a general analysis of the panorama, observing months from January to July, and another to evaluate the effect of social distancing, with April to July. March was the cut-out month because it is the period of implementation of pandemic containment measures in Brazil in 2020 and from April the country with the most impact.[18] To ensure the quality of the collection, two independent authors reviewed the data.

The calculation of the monthly incidence of hospitalizations in the public health system used the formula total number of hospitalizations/population number per age (per year and place [Brazil-IBGE]) x 100,000 inhabitants).[19] Health insurance each year, provided by the National Health Agency, ranged from 20.80% in 2015 to 19.60% in 2020 for the population under 14 during the study period.[20] This percentage was excluded from the denominator, as the population can make use of other hospital means, and hospitalization data are not included in DATASUS. In order to calculate the difference in incidence between pandemic periods with and without containment measures, the incidence rate ratio (IRR) was used to assess statistical significance, with a 95% confidence interval.

RESULTS

Based on hospitalizations in the Unified Health System (SUS), through datasus information, the monthly distribution of the incidence of hospitalizations for laryngitis and acute tracheitis in January to February

was similar, with a tendency to decrease over the study period. (2015-2020). The lowest incidence was observed in January 2016, with 1.32 / 100,000 hospitalizations, and the highest in February 2017, with 2.27 / 100,000 hospitalizations. In the period between March and April, the downward trend was maintained, but with peaks of hospitalizations, mainly in March 2017, with 3.28 / 100,000 hospitalizations, and April 2018, with 3.06 / 100,000 hospitalizations, with the lowest incidence recorded in this period being April 2020, with 0.41 / 100,000 hospitalizations. The month of May, during the years analyzed, remained with a linear pattern and sharp decrease in 2020. The highest incidence was 2.97 / 100,000 in 2018 and the lowest was 0.21 / 100,000 in 2020. June maintained a very close incidence in 2015, 2016, 2017, and 2018, with a fall in incidence in 2019; however, in 2020, the month of June showed a significant drop in this parameter, a drop that had been occurring since April, with 0.41 / 100,000 hospitalizations to 0.21 / 100,000 in May, June, and July. In the period between January and July 2015 to 2020, the incidence of laryngitis and acute tracheitis was 2.42 / 100,000 (2015), 2.17 / 100,000 (2016), 2.42 / 2100,000 (2017), 2.38 / 100,000 (2018), 2.11 / 100,000 (2019), 0.87 / 100,000 (2020), respectively.

Regarding the monthly distribution of the incidence of hospitalizations due to otitis media, the months from January to March presented similar values, with a tendency to increase over the period studied (2015-2020). The lowest incidence was observed in February 2015, with 1.04 /100,000 hospitalizations, and the highest in January 2019, with 1.88 / 100,000 hospitalizations. The months of April and May, during the years analyzed, maintained a linear increase, but a sharp drop in 2020. The highest incidence was 2.01 / 100,000 in 2019 and the lowest was 0.38 / 100,000 in 2020. The same pattern is observed maintained in July, with an increase in incidences from 2015 to 2019, with a higher incidence recorded in 2019, with 1.98 / 100,000, but with a sharp drop in 2020, reaching 0.30 / 100,000. In the period between January and July 2015 to 2020, the incidence of otitis media was 1.30 / 100,000 (2015), 1.41 / 100,000 (2016), 1.55 / 10 000 (2017), 1.56 / 100,000 (2018), 1.86 / 100,000 (2019), 0.87 / 100,000 (2020), respectively, as shown in Table 1.

In the comparison of subsets by macroregions of Brazil on laryngitis and acute tracheitis (April to July 2015 to April to July 2020), there was also a significant reduction in all comparisons. The North region showed the largest reduction in the incidence of hospitalizations, with -94% [IRR 0.05 (0.00 to 0.37)] in 2015-2019 vs 2020. In the Northeast, the reduction ranged from - 91% [IRR 0.09 (0.00 to 1.06)] in 2015-2019 vs 2020. For the Southeast region, there was a reduction of -83% [IRR 0.17 (0.02 to 1.14)] in 2015-2019 vs 2020. The Southern region showed a reduction in incidence ranging from -92% [IRR 0.07 (0.00 to 0.64)] in 2015-2019 vs 2020. In the Midwest region, the variation was -89% [IRR 0.10 (0.01 to 0.61)] in 2015-2019 vs 2020 in the incidence of hospitalizations.

In the subsets by macroregions of Brazil, the comparison with otitis media (April to July 2015 to 2019 vs. April to July 2020), there was a significant and relevant decrease in all comparisons. In the North region, the reduction in the incidence of hospitalizations was -73% [IRR 0.26 (0.03 to 1.94)] in 2015-2019 vs 2020. In the Northeast, the reduction ranged from - 64% [IRR 0.36 (0.06 to 1.96)] in 2015-2019 vs 2020. For the Southeast region, there was a reduction of -80% [IRR 0.19 (0.03 to 1.18)] in 2015-2019 vs 2020. The Southern region showed a reduction in incidence ranging from -83% [IRR 0.17 (0.03 to 0.90)] in 2015-2019 vs 2020. The Midwest region showed the greatest variation, with -85% [IRR 0.15 (0.01 to 1.25)] in 2015-2019 vs 2020 in the incidence of hospitalizations. The absolute total number of hospitalizations, the incidence of hospitalizations per 100,000 inhabitants (0 to 9 years), and the differences between hospitalizations in the period, between 2015 and 2020, are shown in Table 2. Figure 1 summarizes the results found in this study

DISCUSSION

Through data obtained by DATASUS and its analysis over the years in Brazil, this study aims to evaluate the impacts of measures applied to social distancing, in order to reduce the incidence of pediatric hospitalizations in children aged 0 to 9 years due to upper airway infections. Such interventions, implemented by the Brazilian Ministry of Education, to control viral spread in environments such as schools and daycare centers, for example, entered into force on March 17, near the beginning of autumn in the southern hemisphere, where there is usually a significant increase in hospitalizations for laryngitis, acute tracheitis and otitis media in the pediatric population.[4] Furthermore, because of the high population index and that the period of implementation of distance measures coincides with the period in which the causative agents of the diseases mentioned above, epidemiological data have numerous advantages in terms of quality.[21]

Considering data from the Centers for Disease Control and Prevention (CDC), an agency of the U.S. Department of Health and Human Services, hospitalizations for COVID-19 in the pediatric population are extremely unusual, with about 4.1%. These data decrease even more when it comes to the need for a pediatric intensive care unit (IU) for individuals of the same age group, with less than 1%. Such rates have also been observed in other developed countries, such as China, Italy, France, and Spain, which maintain a very similar pattern. In France, for example, François Angoulvant, a pediatric emergency physician, collected information on visits to six emergency rooms of children in Paris from March 2020, when the French government ordered the partial closure of the region on account of the arrival of COVID-19. Data from 871,500 patients between 2017 and 2020 were analyzed, in which hospitalizations

Table 1. Incidence of hospitalizations for Laryngitis, Tracheitis, Otitis Media and malignant neoplasm of bone and articular cartilage from 2015 to 2020 in children under 9 years of age in Brazil.

	Laryngitis and Traqueite*						Otitis Media*						Malignant neoplasm of bone and articular cartilage (Control)*					
	2015	2016	2017	2018	2019	2020	2015	2016	2017	2018	2019	2020	2015	2016	2017	2018	2019	2020
January	1.60	1.32	1.50	1.58	1.47	1.37	1.23	1.30	1.45	1.41	1.88	1.72	0.31	0.28	0.32	0.38	0.37	0.40
February	1.85	1.54	2.27	1.69	1.57	1.72	1.04	1.18	1.22	1.16	1.40	1.55	0.30	0.25	0.25	0.28	0.33	0.30
March	2.96	2.84	3.28	2.84	2.62	1.93	1.27	1.38	1.64	1.66	1.71	1.35	0.36	0.36	0.32	0.24	0.36	0.36
April	2.94	2.90	2.92	3.06	2.80	0.41	1.26	1.52	1.60	1.67	1.87	0.47	0.32	0.33	0.26	0.28	0.35	0.27
May	2.93	2.58	2.60	2.97	2.60	0.21	1.39	1.50	1.61	1.79	2.01	0.38	0.26	0.35	0.35	0.27	0.36	0.31
June	2.69	2.17	2.37	2.54	2.05	0.21	1.41	1.42	1.72	1.51	2.17	0.35	0.30	0.33	0.31	0.29	0.25	0.26
July	2.00	1.85	1.98	1.98	1.68	0.21	1.47	1.57	1.59	1.72	1.98	0.30	0.29	0.40	0.26	0.30	0.33	0.15
Average Jan-July	2.42	2.17	2.42	2.38	2.11	0.87	1.30	1.41	1.55	1.56	1.86	0.87	0.31	0.33	0.30	0.29	0.34	0.29
Δ %	January-July (2015-2019) vs January-July (2020) -62%						January-July (2015-2019) vs January-July (2020) -43%						January-July (2015-2019) vs January-July (2020) -0.06%					

Δ%: percentage change between periods. *Average monthly incidence per 100,000 children.

Table 2. Incidence of hospitalizations for Laryngitis, Tracheitis and Otitis Media from 2015 to 2020 in children under 9 years of age in Brazil and Brazilian macro-regions.

	Laryngite and Tracheite[1]		Relative difference in rate[2]		Otitis Media[1]		Relative difference in rate[2]	
	April-July 2015-2019	April-July 2020	%	IRR (CI)*	April-July 2015-2019	April-July 2020	%	IRR (CI)*
Brazil	9.92	1.05	- 89%	0.10 [0.01 to 0.79]*	6.55	1.50	- 77%	0.22 [0.03 to 1.35]*
North	20.2	1.15	- 94%	0,05 [0,00 to 0,37]*	4.63	1.24	- 73%	0.26 [0,03 to 1,94]*
Northeast	7.65	0.69	- 91%	0.09 [0,00 to 1.06]*	5.05	1.83	- 64%	0,36 [0,06 to 1,96]*
Southeast	7.28	1.25	- 83%	0.17 [0.02 to 1.14]*	7.25	1.41	- 80%	0.19 [0.03 to 1.18]*
South	11.9	0.92	- 92%	0.07 [0,00 to 0,64]*	9.43	1.61	- 83%	0.17 [0.03 to 0.90]*
Midwest	13.1	1.41	- 89%	0.10 [0.01 to 0.61]*	6.55	0.99	- 85%	0.15 [0.01 to 1.25]*

[1]Incidence per 100,000 children. [2]Δ%: percentage change between periods; IRR: Incidence rate ratio; CI: Confidence interval [95%].

in pediatric emergency rooms decreased by 45% during the months of the pandemic.[22] Brazil, in turn, presented, through a recent study, 56% of hospital admissions being in the pediatric population, among which 19% required PICUs in cases of COVID-19; however, this study analyzed reference hospitals of high clinical complexity and, therefore, that obtained patients with multiple comorbidities, which may be the reason for such a sharp deviation when compared to studies in more developed countries. Although a 2020 Hoang et al.systematic review identified co-infection in 6% of cases of pediatric hospitalization with Mycoplasma pneumonia and Respiratory Sincicial Virus, many studies point to a significant decrease in several regions of the world in dealing with the diseases mentioned and their respective hospitalizations in pediatrics.[23] The study Yeoh et al.[24]) analyzed the pediatric population of Australia and showed reductions of 98.0% and 99.4% in RSV and influenza detections, respectively, until the winter of 2020; as well as a study conducted in Belgium showed a decrease of >99% in the recorded cases of RSV in 2020 compared to previous years.[25] This fact may be closely linked because the transmissibility of respiratory agents decreased due to isolation measures, with a general awareness of the need for proper handwashing, use of alcohol gel, regular cleaning of toys, individual use of utensils and personal masks, in addition to the closure of schools and sports clubs proposed by the Brazilian government.[26,27] Therefore, all the measures mentioned may have contributed to the reduction of laryngitis, tracheitis, and acute otitis media in children, reducing interpersonal contact and greater care for personal hygiene.

According to the Brazilian Society of Pediatrics, it is necessary to have careful maintenance of care for children and adolescents even in times of pandemics. According to data from FIOCRUZ - the main non-university institution for the training and qualification of human resources for the SUS and the area of science and technology in Brazil[28] - in 2020 some health units recorded a reduction in the number of outpatient care of up to 90% between March and July 2020, when compared to the same period in 2019, causing several losses to the patient and future overcrowding in the country's health services.[23] This fact was also analyzed through a recent multicenter study, which showed that emergency visits and hospital admissions were greatly reduced during COVID-19 blockades in the Netherlands, as in the rest of the world, especially for children with transmissible infections.[29] Although it is widely known that this period of isolation has brought health problems when it comes to routine visits or monitoring of chronic diseases, it is possible to note that the measures proposed by the guidelines for the control of transmission of SARS -CoV-2 infection have had an impact on other etiological agents, which are related to pediatric laryngitis, acute tracheitis and otitis media due to the forms of contagion.[27,30,31] That is, although this factor can be seen as confounding, it cannot be said as a direct or isolated influence on the results found in our study, because, as observed in previous studies, our main hypothesis is that non-pharmacological health measures to contain the COVID-19 pandemic have a significant impact on the spread of several respiratory viruses that still have a lower propagation potential than SARS-CoV-2.

There was a sharp decrease in hospitalization rates between March and July 2020 in all Brazilian macro-regions, during which restrictive measures were implemented.[2] Our findings show that, annually, the incidence of hospitalizations for laryngitis, acute tracheitis, and otitis media increases, as occurs in countries in other developing countries, such as Brazil. However, it is noted that there was a drastic reduction in the incidence of pediatric hospitalizations for upper airway infections in the period from 2015-19 to 2020 from March when in Brazil social distancing due to COVID-19 began.

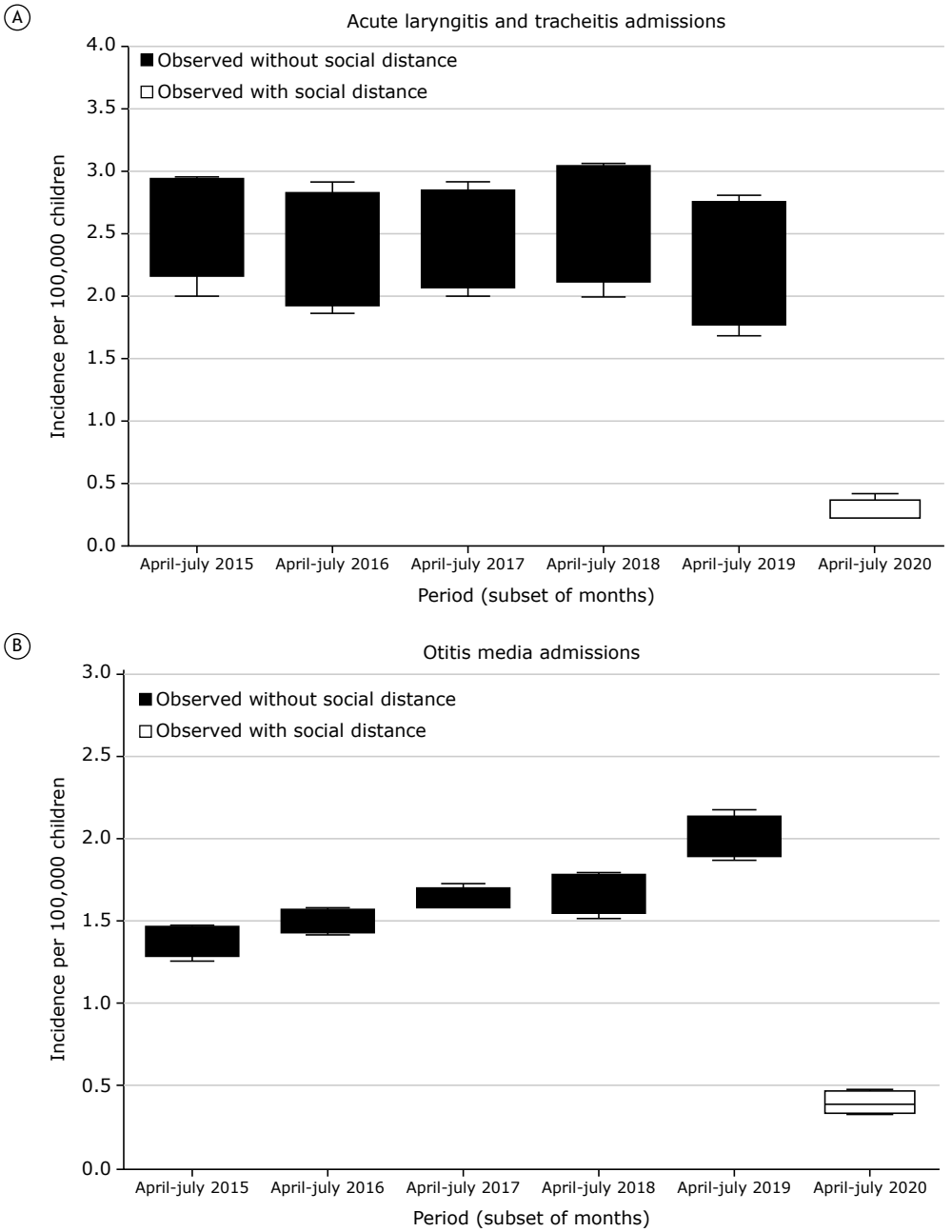

Figure 1. Distribution of the incidence of hospitalizations for Laryngitis, Tracheitis, Otitis Media in Children observed with and without social distancing (2015-2020).

Before this period, that is, in January and February 2020, there was a similar incidence over the years, with an exponential increase in hospitalization cases considering the seasonality of the disease in the country.[32] For hospitalizations for laryngitis and acute tracheitis, the data suggest a downward trend over the study period (2015-2020). The lowest incidence occurred in April 2020, and this significant reduction was maintained in May and June. In hospitalizations for acute otitis media, there was an upward trend in the period from 2015 to 2020. The months of January to March maintained similar values, but from April to July, the increase observed until 2019 was interrupted by a sharp drop in the year 2020. In the comparison between the Brazilian macroregions, the North region showed a greater reduction in hospitalizations for laryngitis and acute tracheitis (-94%). Secondly, the South region decreased -92%, followed by the Northeast (-91%), Midwest (-89%), and Southeast (-83%). As for hospitalizations due to acute otitis media, there was

a marked decrease in all the comparations, the most significant in the Midwest region (-85%). The South region fell -83% and was followed by the Southeast (-80%), North (-73%), and Northeast (-64%).

Finally, the present retrospective study, however, has some limitations, such as the impossibility of evaluating isolated non-pharmacological interventions, because they were implemented simultaneously. In terms of data collection, another limitation is about the platform, because they were filled out by third parties, DATASUS employees, and not by the researchers who wrote it, considering the pandemic period and social distance. Data were collected for each month with a delay of two months and, according to our previous experiences, this period is sufficient for DATASUS to update the final numbers or the very approximate values, considering that the data are included according to the forms of Hospitalization Authorizations, in Brazil AIH (Hospital Admission Authorization). Still in this regard, the data present population nature, with robust national and regional epidemiological information, taking into account the population size, which reiterates the findings and presents as an advantage concerning the other studies.[33,34] Moreover, when analyzing hospitalizations for otitis, we are only covering severe cases, considering that the mildest and most common cases receive outpatient treatment, which may represent a bias in terms of estimating the real fall in the incidence of this infection. However, and there are such limitations, we consider that these results truly reflect the current moment, considering that these were the same throughout the evaluation period, which reinforces the validity of the main findings of the present study. Such changes in the profile of pediatric hospitalizations, in terms of epidemiology, had not been reported before in Brazil.

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AUTHOR CONTRIBUTIONS

CRJ participated in the study planning, coordinated data collection and wrote the article. AASR, ASM, ACA, FBM, SMF, LCSM participated in the planning, data collection and writing of the first version of the paper. Frederico Friedrich participated in the analysis and final writing of the article. LAP coordinated the study planning, data collection and final writing of the article.

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ORIGINAL ARTICLE

Transition from APAP to CPAP may be a cost-effective health intervention in OSA patients

Adelaide Alves[1], Ana Rita Gigante[1], Daniela Machado[1], Inês Sanches[1], Raquel Marçoa[1], Inês Franco[1], Regina Monteiro[1], Carla Nogueira[1], Daniela Ferreira[1]

1. Departamento de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Porto, Portugal.

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Study carried out at the Unidade do Sono, Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal.

ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a common disorder associated with a significant economic burden. Continuous positive airway pressure (CPAP) and auto-titrating positive airway pressure (APAP) are recognized therapeutic options in patients with OSA, although treatment costs are higher with APAP. We conducted a study aimed at evaluating the effectiveness and potential cost savings resulting from the implementation of a protocol guiding the transition to CPAP in OSA patients previously treated with APAP. **Methods:** This prospective study included patients with OSA under APAP who were followed up at the Sleep Medicine outpatient clinic of a tertiary referral hospital between January 2019 and January 2021. Treatment was switched to CPAP in patients who met the following criteria: satisfactory adaptation and adherence to APAP, residual apnea-hypopnea index (AHI) of < 5/hour, and no relevant air leaks. APAP and CPAP outcomes were compared and an estimate of the savings obtained by the transition from APAP to CPAP was calculated. **Results:** Ninety-three patients were included in the study. APAP and CPAP were both effective in correcting obstructive events and improving daytime sleepiness. No significant differences were found regarding treatment adherence and tolerance between both PAP modalities. The selection of fixed-pressure CPAP through 90th or 95th percentile APAP pressure proved to be effective and an alternative strategy to titration polysomnography. At the end of this two-year study, the transition from APAP to CPAP enabled savings of at least 10,353€. **Conclusion:** The transition from APAP to CPAP may be an effective, well-tolerated, safe, and cost-saving strategy in patients with OSA.

Keywords: Obstructive sleep apnea (OSA); continuous positive airway pressure (CPAP); auto-titrating positive airway pressure (APAP); health care costs

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder that affects 9% to 38% of the overall population.[1] The reported prevalence of OSA has escalated concerningly over time, in part due to the increasing number of obese patients, in whom the prevalence exceeds 30%.[2] OSA is an emerging major health problem since it is a recognized, independent risk factor for cardiovascular, metabolic, and psychiatric disorders.[3,4] High disease burden is also related to excessive daytime sleepiness, impaired quality of life, workplace and motor vehicle accidents, losses in productivity, and health care costs.[5,6]

Positive airway pressure (PAP) is the treatment of choice for OSA and may be delivered through continuous positive airway pressure (CPAP) or auto-titrating positive airway pressure (APAP).[7] CPAP delivers constant positive pressure to the upper airway during sleep, preventing its collapse.[8,9] On the other hand, APAP delivers variable pressure depending on changes in airflow resistance, which may vary according to several factors, including the stage of sleep, body position, and the degree of nasal congestion.[10,11] The effects of treatment seem similar between CPAP and APAP and, for that reason, the therapeutic choice often relies on other factors, such as patient preference, specific reasons for non-compliance, and direct and indirect costs.[12,13]

Titration polysomnography (PSG), performed in sleep laboratories, is the gold standard approach to determine optimal PAP levels but is associated with high costs and long waiting lists.[7] Previous studies have shown that the 90th or 95th percentile pressure level obtained through APAP tracking system registration has a good correlation with the PAP levels obtained through titration PSG; this approach is more cost-effective compared to manual laboratory titration.[14,15] In patients treated with APAP, after identifying the most suitable fixed pressure that corrects respiratory events through the 90th or 95th percentile, it is possible to modify treatment to CPAP using that specified level of pressure.

In the Portuguese National Health System, the initial prescription of CPAP or APAP is conducted in Sleep Medicine Centers by pulmonologists, who ensure the diagnostic work-up and therapeutic decision of patients with OSA. Following medical prescription, home respiratory care companies then provide the CPAP or APAP device, and the treatment is entirely

Correspondence to:
Adelaide Alves. Departamento de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Porto, Portugal.

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paid for by the National Health System. Although both are effective in treating OSA, CPAP and APAP have different costs, which are higher with APAP. In Portugal, the contractual prices agreed between the National Health System and home respiratory care companies are 1.0399€/day with CPAP and 1.2079€/day with APAP.[16] In addition, for patients who choose to buy their own PAP machine, the cost of the APAP device is typically higher than that of CPAP. On the other hand, for OSA patients with health insurance, many companies may not approve APAP coverage due to its higher cost when compared to CPAP.

In this study, we aimed to evaluate the effectiveness and potential cost savings resulting from the transition from APAP to CPAP in patients with OSA followed up in a Sleep Medicine outpatient clinic of a tertiary referral hospital in northern Portugal.

METHODS

Study Design and Data Collection

The present prospective, single-center study included adult patients with previously diagnosed OSA, treated with APAP, who were followed up at the Sleep Medicine outpatient clinic of the Vila Nova de Gaia/Espinho Hospital Center, in Portugal, between January 2019 and January 2021. Data collection and analysis were conducted in February 2021.

All patients were evaluated by a pulmonologist with expertise in sleep medicine. After an initial and variable period of treatment with APAP, the patients were switched to CPAP treatment. The transition of the treatment from APAP to CPAP was carried out in patients who met the following criteria: satisfactory adaptation to APAP, good adherence to treatment (use for > 4 hours/night in at least 70% of the nights), residual apnea-hypopnea index (AHI) of < 5/hour, and no relevant air leaks (leak in the 95th percentile < 25L/min). Informed consent was obtained from all patients, and the study protocol was approved by the ethics committee of the Vila Nova de Gaia/Espinho Hospital Center.

The PAP devices were chosen by the home respiratory care companies, providing they were suitable for medical prescription (S9 AutoSet™ or AirSense 10 AutoSet™ from ResMed, or SystemOne™ or DreamStation™ from Philips Respironics). Treatment was started with a nasal interface; if the patient complained of discomfort or intolerance or required better air leak control, treatment was changed to an oronasal interface. Humidifiers and heated circuits were prescribed both with APAP or CPAP when needed for patient comfort.

Patients were excluded if any of the following criteria were present: poor adaptation or compliance to APAP treatment, hypoventilation disorders, a predominance of central events, cognitive disability, and incomplete medical data.

The number of hours that the PAP device was used per night, the percentage of nights the PAP device was used for more than 4 hours, residual AHI, and air leak were established through machine-recorded compliance data. Regarding APAP, data was collected in the three months prior to CPAP transition. CPAP data was collected after three months of treatment.

Definitions

The diagnosis of OSA was obtained with PSG conducted in the hospital (level 1) or on an outpatient basis (level 2) or by home cardiorespiratory polygraphy (level 3). Sleep studies were manually scored by an experienced sleep technician according to the criteria of the American Academy of Sleep Medicine.[17] The diagnosis was established based on the criteria of the third edition of the International Classification of Sleep Disorders,[18] and OSA severity was defined as mild for AHI of ≥ 5/hour and < 15/hour, moderate for AHI of ≥ 15/hour and ≤ 30/hour, and severe if AHI > 30/hour. Positional OSA was defined as a total AHI of ≥ 5/hour, with a > 50% reduction in the AHI between the supine and nonsupine positions. Rapid eye movement (REM) sleep-related OSA was defined as the occurrence of obstructive apneas and hypopneas predominantly or exclusively during REM sleep in patients who underwent PSG.

Statistical Analysis

A descriptive analysis was performed. Normality was tested using the Shapiro-Wilk test. Continuous variables were described using mean and standard deviation or median and interquartile range (IQR). Categorical variables were expressed as frequencies (n) and percentages (%). For the analyses of repeated measurements in a single sample, Wilcoxon's signed-rank test was applied for continuous variables, and McNemar's test was performed for categorical variables. All statistical analyses were carried out with the Statistical Package for the Social Sciences (SPSS)® program (Chicago, Illinois, USA), version 22.0. The level of statistical significance was set at $p < 0.05$.

RESULTS

Study population

In a total of 209 patients with OSA undergoing APAP therapy, 93 were included based on the selection criteria. The reasons underlying participant exclusion from the study were: poor APAP compliance (n = 81), residual AHI of > 5/h under APAP therapy (n = 19), associated hypoventilation disorders (n = 11), and significantly incomplete medical records (n = 5). Most patients were male (76.3%), and the median age was 61 [51 - 67] years. A significant prevalence of cardiovascular disease was observed, namely arterial hypertension (66.7%), obesity (52.7%), dyslipidemia (41.9%), and heart failure (26.9%). Most patients (78.5%) had moderate or severe OSA, with a median AHI of 25.1/hour [16.9 - 41.0]. The

demographic and clinical characteristics of the patients are summarized in Table 1.

PAP outcomes

After starting treatment with APAP, the median time until CPAP transition was 18 [8 - 36] months. The median APAP minimum and maximum pressures were 6 [5 - 6] cmH_20 and 12 [12 - 14] cmH_20, respectively. APAP was effective in eliminating sleep respiratory events, resulting in a median residual AHI of 1.7/hour [0.9 - 2.8]. Although patients presented good adherence to APAP (median use of 7 hours/night and use for > 4 hours/night in 93% of the cases), 61.3% exhibited side effects related to therapy, namely mucosa dryness (49.5%), nasal congestion (11.8%), feeling of air leak (7.5%), cold feeling (5.4%), and facial pain (5.4%). Mucosa dryness and cold feeling were solved with humidifiers and heated circuits, respectively, in all patients who reported these side effects.

In 97.8% of the patients, optimal pressure determination for CPAP treatment was conducted based on the 90th or 95th percentile pressure level identified in the last APAP therapy report. In 2.2% of the patients, the determination of CPAP pressure was based on titration PSG, performed in the sleep laboratory. The median initial CPAP pressure was 10 [9 - 11] cmH_20. Pressure adjustment was required in 16.1% of the patients due to intolerance to high pressure (33.3%), controlled residual AHI, enabling pressure reduction (26.7%), high air leak (20%), and uncontrolled residual AHI, requiring pressure increase (20%). The median final CPAP pressure was 9 [8 - 11] cmH_20.

The comparison between APAP and CPAP therapy is shown in Table 2. Both were equally effective in improving daytime sleepiness, a hallmark symptom of OSA, as indicated by the Epworth Sleepiness Scale (ESS). The percentage of patients with at least one side effect was statistically lower with CPAP than with APAP (32.6% *vs*. 60.9%; $p < 0.001$); they included mucosa dryness (20.4%), feeling of air leak (8.6%), nasal congestion (n = 6; 6.5%), feeling of high pressure (3.2%), and aerophagia (1.1%). It is noteworthy that CPAP was statistically superior to APAP in controlling the residual AHI (1.4/h *vs*. 1.7/h; $p = 0.033$), although both therapies were effective.

Table 1. Demographic and clinical characteristics of the patients.

Baseline characteristics	Study population (n = 93)
Age, years	61 [51-67]
Male	71 (76.3)
BMI, kg/m^2	30.2 [26.6-33.9]
Neck circumference, cm	42.6±3.66
Mallampati score	
I	10 (10.8)
II	7 (7.5)
III	20 (21.5)
IV	18 (19.4)
N/A	38 (40.9)
Comorbidities	
Obesity	49 (52.7)
Arterial hypertension	62 (66.7)
Diabetes mellitus	21 (22.6)
Dyslipidemia	39 (41.9)
Atrial fibrillation	8 (8.6)
Heart failure	25 (26.9)
History of stroke	5 (5.4)
Baseline ESS score	11.5 [6-15]
Sleep study	
Level 1	35 (37.6)
Level 2	16 (17.2)
Level 3	42 (45.2)
OSA Severity	
Mild	20 (21.5)
Moderate	36 (38.7)
Severe	37 (39.8)
AHI, n/hour	25.1 [16.9-41]
T90, min	18 [4-62]
Positional OSA	15 (16.1)
REM-related OSA (n=51)*	6 (11.8)

Data are presented as n (%) or mean ± SD or median [interquartile range]; N/A – not available. *Only patients who underwent a level 1 or 2 sleep study. AHI: apnea-hypopnea index; BMI: body mass index; OSA: obstructive sleep apnea; REM: Rapid eye movement; T90: total sleep time spent with arterial oxygen saturation < 90%.

Sub-analysis including patients with positional or REM-related OSA revealed no statistically significant differences between APAP and CPAP outcomes, except in the subgroup of patients with positional OSA, in which the number of hours of therapy per night was greater with CPAP than with APAP (7.5h *vs*. 6.7h; $p = 0.046$). It should also be noted that in patients with positional OSA, residual AHI tended to be higher in those treated with CPAP than with APAP (6.8/h *vs*. 2.3h; $p = 0.374$).

After switching treatment to CPAP, most (91.4%) patients maintained good tolerance. However, in 8.6% of the patients, CPAP was poorly tolerated, mostly because of mucosa dryness (50%) and feeling of nasal obstruction (25%). The treatment needed to be switched again to APAP in 5.4% of the patients due to the occurrence of side effects, and in one patient with OSA and chronic obstructive pulmonary disease (COPD) overlap syndrome, the treatment was changed to bilevel positive airway pressure (BPAP) on account of persistent daytime hypercapnia, despite controlled residual AHI.

Among all patients, 33.3% were discharged to Primary Health Care since they had good adherence and tolerance to CPAP, with clinical benefit and corrected nocturnal respiratory events. None of these patients were referred to the Sleep Medicine Center again during the follow-up period of this study. Loss of follow-up was observed in five (5.4%) patients.

The mean time between the beginning of CPAP treatment and the end of the study was 22.8 ± 7.7 months. Based on the contractual costs of PAP therapy in Portugal, the transition from APAP to CPAP enabled a mean savings of 119 ± 39.11€ per patient and, at the end of this two-year study, including 87 patients who remained under CPAP treatment, an amount of 10,353.84€ was saved.

DISCUSSION

In the present study, both PAP modalities were effective, allowing the correction of nocturnal obstructive events and the improvement of subjective sleepiness, as measured by the ESS. Indeed, CPAP was statistically superior to APAP in the correction of residual AHI. Still, the clinical meaning of this finding is probably irrelevant, as both therapies enabled to achieve a residual AHI of < 5/hour. Our results are in line with previous studies documenting that both APAP and CPAP are similar in their ability to eliminate respiratory events and improve daytime OSA-related symptoms.[12,13]

Patients showed good tolerance to APAP and CPAP, although side effects tended to be less frequent with the latter. It is noteworthy, however, that the occurrence of fewer side effects with CPAP might be explained by the fact that they could have been previously identified and corrected during the initial treatment with APAP. With both PAP modalities, side effects were mainly minor and reversible. Unlike previous studies revealing that APAP was better tolerated and more effective than CPAP in increasing patient compliance, we found no differences between both therapies regarding treatment tolerance and adherence.[19,20]

In daily clinical practice, the pressure chosen for CPAP is frequently selected using the automatic algorithm of APAP devices.[12,13,21] Here, the choice of CPAP pressure was based on the 90th or 95th percentile APAP pressure in most cases; this strategy proved effective since CPAP pressure readjustment was needed in only 16.1% of the patients and in none

Table 2. PAP treatment outcomes.

Overall patients (n = 93)	APAP	CPAP	p-value
Residual AHI, n/hour	1.7 [0.9-2.8]	1.4 [0.6-2.2]	0.033*
Use > 4 hours, % of nights	93.3 [86.7-98]	93 [83.6-98.9]	0.370
Mean use, hours/night	7 [6-8]	7 [6-8]	0.121
Side effects	56 (60.9)	30 (32.6)	<0.001*
ESS post-PAP	3 [3-5]	3 [3-4]	0.625
Positional OSA (n=15)	APAP	CPAP	p-value
Residual AHI, n/hour	2.3 [1.4-3.5]	6.8 [6-8]	0.374
Use > 4 hours, % of nights	92.4 [85-98.9]	89 [84.4-98]	0.092
Mean use, hours/night	6.65 [5-7.5]	7.5 [6.5-8]	0.046*
Side effects	8 (57.1)	4 (28.6)	0.219
ESS post-PAP	3 [3-6]	4 [4-5]	0.630
REM-related OSA (n=51)	APAP	CPAP	p-value
Residual AHI, n/hour	2.25 [1.6-2.8]	1.9 [0.8-2.8]	0.344
Use > 4 hours, % of nights	93.05 [84.5-98.9]	91.5 [73.3-96.1]	0.225
Mean use, hours/night	7.25 [6.5-7.75]	7.5 [6.25-8.25]	0.854
Side effects	3 (50)	1 (16.7)	0.625
ESS post-PAP	4 [3-6]	4 [4-6]	0.633

Data are presented as n (%) or median [interquartile range]; *p-value <0.05. AHI: apnea-hypopnea index; APAP: auto-titrating positive airway pressure; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale; OSA: obstructive sleep apnea; PAP: Positive airway pressure; REM: Rapid eye movement.

of them was overnight PSG necessary, a relevant finding given the costs and difficult access to the sleep laboratory. The possibility of defining CPAP optimal pressures through APAP device-recorded data is a window of opportunity for the use of telemedicine in OSA patients. In fact, there are devices on the market designed to automatically measure the ideal PAP level, switching remotely from the APAP mode to CPAP mode after a period of time.[22] This available resource may not only improve the follow-up of patients with OSA but also enable telehealth instead of conventional face-to-face clinical visits, which may be a valuable alternative in the era of the Coronavirus Disease 2019 (COVID-19) pandemic. At the same time, regardless of the pandemic context, telehealth and telemonitoring remain useful tools since patients with OSA are typically a working population, and, for that reason, this alternative to conventional visits allows them to save time and resources and avoid absences from work.

At the end of the study, the median final CPAP pressure was lower than the initial pressure. This might be explained by the fact that the most frequent reasons for pressure readjustment were intolerance to high pressure and controlled residual AHI, allowing pressure reduction. In addition, a delayed effect of CPAP has also been previously described.[23] The effective CPAP level may progressively decrease with time, which can be attributed to an improvement in upper airway morphology and/or the correction of sleep fragmentation, which we can speculate that may also have contributed to a lower median final CPAP pressure in our study.[24,25,26]

It has been previously demonstrated that only one week of APAP therapy seems sufficient to determine an effective and stable PAP level within the pressure range of ± 2 cmH_20.[21] However, in the current study, we verified a longer time from the beginning of APAP until the transition to CPAP (18 [8 - 36] months). This finding may be explained by the fact that some patients were already under treatment with APAP for a long time, and the transition to CPAP was only conducted because of patient inclusion in this study. This finding may somehow suggest that doctors are not fully aware of the effectiveness, safety, and cost savings of the transition from APAP to CPAP in their daily clinical practice.

It is well known that the required level of pressure to eliminate obstructive respiratory events varies overnight depending on several factors, such as body position, sleep state, nasal obstruction, and the use of alcohol and hypnotic agents.[10,11,14] APAP could be a more attractive PAP modality if such pressure requirement variability were resolved. Nonetheless, in this study, we found that the benefits of the transition from APAP to CPAP remained, even in the subgroup of patients with positional OSA and REM-related OSA. However, patients with positional OSA under CPAP treatment presented a median residual AHI of 6.8/hour, slightly above the desired value (< 5/hour). It is important to note that a small number of patients was included in the subgroup of positional OSA and that there was no statistically significant difference between APAP and CPAP with regard to residual AHI. Nevertheless, this data may suggest that patients with positional OSA may not be good candidates for switching from APAP to CPAP. Additionally, in this study, REM-related OSA was probably underdiagnosed, given that in 45.2% of the patients, PSG was not performed.

To the best of our knowledge, this is the first study evaluating the effectiveness and potential cost savings with the transition from APAP to CPAP in a population of OSA patients. Assessing the cost-effectiveness of health interventions is an essential guide for public health decision-making in order to better decide the allocation of economic resources. Impressively, in the present study, the implementation of a protocol guiding the transition from APAP to CPAP in a relatively small population of OSA patients allowed savings of nearly 10,350€ in only two years. We believe that our results raise important questions in daily clinical practice, given that OSA is a prevalent chronic disease and PAP is a treatment for life, imputing huge costs to healthcare systems. Furthermore, it should also be noted that, in some countries, after discharge from hospital consultation, Primary Health Care physicians renew chronic PAP prescriptions, but they cannot change them; therefore, awareness regarding the transition from APAP to CPAP must exist at the level of Sleep Medicine Centers. Moreover, if we take the chronicity of PAP therapy, the relatively young age of OSA patients, and the increasing worldwide average life expectancy into account, the savings potential would be even more significant.[27]

Our results encourage the development and implementation of protocols guiding the transition from APAP to CPAP in OSA patients at the level of Sleep Medicine Centers. To this end, appropriate human and technical resources must be allocated, including the use of telehealth.

This study presented some limitations. Among the 209 patients recruited initially, only 93 were included, indicating that we could be facing a selection bias. This fact may limit the generalizability of the conclusions drawn herein since the transition to CPAP was conducted in a very specific population of OSA patients with good compliance, acceptable tolerance, and correction of obstructive events under APAP therapy. Thus, we can speculate that, in OSA patients, APAP - through its ability to automatically adjust the air pressure throughout the night - is a suitable initial therapeutic strategy with the intention of later switching treatment to CPAP, an equally effective but less expensive therapeutic option. On the other hand, although our results demonstrate the potential savings obtained from the transition from APAP to CPAP, a real cost-effectiveness analysis was not carried out. In addition, the potential savings resulting from the selection of the CPAP pressure through the 90th or 95th percentile APAP pressure instead of titration

PSG were not taken into account. Another limitation of this study was the relatively short follow-up of the patients included. In fact, because of this limitation, it may be difficult to ascertain if the fixed pressure defined in the CPAP before hospital discharge will remain suitable throughout the patient's life since weight variations and anatomical changes in the upper airways due to aging may occur. For this reason, after discharge to Primary Health Care, OSA symptoms and the compliance report, namely residual AHI, should be regularly assessed in order to identify the need for a new referral to hospital consultation. Finally, this study has limited generalizability to the overall OSA population since it was conducted in a single Portuguese center, and both treatment costs and OSA patients' management can be significantly different in other settings, namely in other countries. A randomized, single-blind, crossover trial evaluating efficacy, compliance, side effects, and patient satisfaction would allow us to draw more definitive conclusions.

The present study shows that the transition from APAP to CPAP may be an effective, well-tolerated, safe, and cost-saving strategy in patients with OSA. The routine implementation of a systematic and uniform guiding protocol with established criteria for the transition from APAP to CPAP in Sleep Medicine Centers potentially enables relevant savings for healthcare systems while maintaining PAP treatment quality.

AUTHOR CONTRIBUTIONS

AA: study conception and design; materials or referral of patients; data collection/assembly; data analysis and interpretation. ARG: data collection/assembly; data analysis and interpretation. DM, IS, and DF: study conception and design; materials or referral of patients. RM, IF, RM, and CN: materials or referral of patients. All authors: drafting and revision of the manuscript.

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Spirometry for the diagnosis of airway obstruction in patients with risk factors for COPD: the GOLD and lower limit of normal criteria

Monica Grafino[1], Filipa Todo-Bom[1], Ana Cristina Lutas[1], Jorge Cabral[2], Marco Pereira[1], João Valença[1], Sofia Tello Furtado[1]

1. Departamento de Pneumologia, Hospital da Luz Lisboa, Lisboa, Portugal.
2. Departamento de Matemática, Universidade de Aveiro, Aveiro, Portugal.

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ABSTRACT

Objective: The identification of persistent airway obstruction is key to making a diagnosis of COPD. The GOLD guidelines suggest a fixed criterion—a post-bronchodilator FEV_1/FVC ratio < 70%—to define obstruction, although other guidelines suggest that a post-bronchodilator FEV_1/FVC ratio < the lower limit of normal (LLN) is the most accurate criterion. **Methods:** This was an observational study of individuals ≥ 40 years of age with risk factors for COPD who were referred to our pulmonary function laboratory for spirometry. Respiratory symptoms were also recorded. We calculated the prevalence of airway obstruction and of no airway obstruction, according to the GOLD criterion (GOLD+ and GOLD−, respectively) and according to the LLN criterion (LLN+ and LLN−, respectively). We also evaluated the level of agreement between the two criteria. **Results:** A total of 241 individuals were included. Airway obstruction was identified according to the GOLD criterion in 42 individuals (17.4%) and according to the LLN criterion in 23 (9.5%). The overall level of agreement between the two criteria was good (κ = 0.67; 95% CI: 0.52-0.81), although it was lower among the individuals ≥ 70 years of age (κ = 0.42; 95% CI: 0.12-0.72). The proportion of obese individuals was lower in the GOLD+/LLN+ category than in the GOLD+/LLN− category (p = 0.03), as was the median DL_{CO} (p = 0.04). **Conclusions:** The use of the GOLD criterion appears to be associated with a higher prevalence of COPD. The agreement between the GOLD and LLN criteria also appears to be good, albeit weaker in older individuals. The use of different criteria to define airway obstruction seems to identify individuals with different characteristics. It is essential to understand the clinical meaning of discordance between such criteria. Until more data are available, we recommend a holistic, individualized approach to, as well as close follow-up of, patients with discordant results for airway obstruction.

Keywords: Pulmonary disease, chronic obstructive; Airway obstruction; Spirometry.

INTRODUCTION

As is well known, COPD is a leading cause of mortality and morbidity worldwide. According to the GOLD, COPD is characterized by persistent respiratory symptoms and airway obstruction, defined as an FEV_1/FVC ratio < 70%.[1] However, the FEV_1/FVC ratio is influenced by sex and age.[2,3] The fixed cutoff value does not reflect that influence and may misclassify airway obstruction. In view of that, some authors have proposed using the lower limit of normal (LLN), estimated from a reference population that is representative (in terms of age, sex, height, and race), as a more accurate criterion to define airway obstruction.[4-6]

The true prevalence of COPD is unknown, and its reported prevalence varies considerably across the world due to differences in survey methods, sample characteristics, and diagnostic criteria.[7-10] Most studies of COPD have been population-based studies including large proportions of individuals without risk factors for COPD (asymptomatic individuals and nonsmokers), have not included post-bronchodilator assessments, or have had both of those issues.[7,9]

The aim of this study was to assess the prevalence of COPD according to the two different criteria used in order to define airway obstruction (FEV_1/FVC ratio < 70% and FEV_1/FVC ratio < LLN), as well as to determine the agreement between those two criteria, in a sample of patients with risk factors for COPD. We also assessed the clinical and functional differences between the patients in whom the criteria were concordant and those in whom they were discordant.

METHODS

Sample

This was an observational study including individuals ≥ 40 years of age who presented with key indicators of COPD and underwent spirometry between September

Correspondence to:
Monica Grafino. Hospital da Luz Lisboa, Avenida Lusíada, 100, 1500-650, Lisboa, Portugal.
Tel.: 35 19 6122-8426. E-mail: mgrafino@gmail.com
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and December of 2019 at the Pulmonary Function Laboratory of the *Hospital da Luz Lisboa*, in the city of Lisbon, Portugal. The key indicators of COPD were defined as follows: a smoking history of ≥ 10 pack-years or a history of relevant exposure to dust, vapor, fumes, gases, or chemicals; or chronic respiratory symptoms, including chronic cough, chronic sputum production, dyspnea—defined as a modified Medical Research Council (mMRC) dyspnea scale score ≥ 2[11]—recurrent lower respiratory tract infections, and wheezing, in a smoker. Individuals who were under treatment with a bronchodilator—long-acting (< 24 h) or short-acting (< 8 h)—were excluded, as were those with a history of asthma, bronchiectasis, interstitial lung disease, or lung resection, as well as those whose symptoms could not be assessed.

The sample size was calculated on the basis of a confidence level of 95% (confidence limits of 5%) and an anticipated frequency in the general population of 14.2%.[12] Thus, the minimum sample size was determined to be 187 subjects.

Demographic characteristics (sex and age), anthropometric data (weight and height), and medical history (smoking habits, history of lung disease, and respiratory symptoms such as chronic cough, chronic sputum production, dyspnea, and wheezing) were obtained from medical records or from the patients themselves, in interviews. Individuals who had quit smoking six months prior to the interview were categorized as former smokers.

Pulmonary function testing

The pulmonary function tests included the determination of FEV_1, FVC, and the FEV_1/FVC ratio. If total body plethysmography, with or without single-breath diffusion testing, was performed, RV, TLC, and DL_{CO} (% of predicted) were also recorded, as recommended in international guidelines.[13-15] All pulmonary function tests were performed by certified respiratory technologists trained in the use of the Masterscreen Body/Diffusion system with SentrySuite Software, version 2.21 (Vyaire Medical Inc., Chicago, IL, USA). Hygiene and infection control measures were applied in all patients. Calibration checks were performed, and quality control procedures were followed. All patients were informed about which activities and medications should be avoided or suspended before the pulmonary function tests.

The Global Lung Initiative (GLI) 2012 reference equations were applied for spirometry,[16] and the European Community for Coal and Steel equations were applied for static volumes.[2] All individuals with a pre-bronchodilator FEV_1/FVC ratio < 70% or < LLN underwent bronchodilator reversibility testing, in accordance with international guidelines.[15,17]

The default bronchodilator was albuterol, administered with a metered dose inhaler (100 µg per actuation). A dose of 400 µg was delivered with a valved holding chamber. Post-bronchodilator FEV_1 and FVC were measured 15 min later, the maneuvers being repeated until three acceptable measurements had been obtained. If albuterol was contraindicated, the anticholinergic agent ipratropium bromide (at a total dose of 160 µg with a valved holding chamber) was used. For the individuals receiving ipratropium bromide, the post-bronchodilator maneuvers were performed at 30 min after administration.

Airway obstruction was defined according to the fixed ratio (GOLD criterion) as a post-bronchodilator FEV_1/FVC ratio < 70% and according to LLN criterion as a post-bronchodilator FEV_1/FVC ratio < LLN (designated GOLD+ and LLN+, respectively). Conversely, a post-bronchodilator FEV_1/FVC ratio ≥ 70% was designated GOLD− and a post-bronchodilator FEV_1/FVC ratio ≥ LLN was designated LLN−. The LLN was calculated by using the GLI 2012 equations,[16] in which it is the overall mean predicted value (based on sex, age, race, and height) minus 1.64 times the standard error of the estimate determined in the population-based study on which the reference equation is based (LLN 5% [lower 5th percentile]; z-score, −1.64).

The study was approved by the Ethics in Clinical Research Committee of the *Hospital da Luz Lisboa*. All participants provided written informed consent.

Statistical analysis

A descriptive analysis of the data was performed with RStudio, version 1.3.1056, running R, version 4.0.2 (RStudio Inc., Boston, MA, USA). Quantitative variables were expressed as medians and interquartile ranges, whereas qualitative variables were expressed as absolute and relative frequencies. The Shapiro-Wilk test was used in order to assess the normality of variables. The level of agreement between the two criteria applied to define airway obstruction was assessed by calculating Cohen's kappa statistic (κ). We defined four categories of agreement between the two criteria: GOLD−/LLN−, GOLD+/LLN−, GOLD+/LLN+, and GOLD−/LLN+. To evaluate between-category differences for the quantitative variables, we used the Kruskal-Wallis test and Dunn's test with Benjamini-Hochberg correction, whereas we used chi-square tests with Benjamini-Hochberg correction to determine whether there were statistically significant between-category differences for the qualitative variables. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Our study sample included 241 individuals, of whom 134 (55.6%) were male. The median age was 60 years, and the median BMI was 27 kg/m^2. All of the individuals had a history of smoking, and 136 (56.4%) were still active smokers. Symptoms were present in 105 (43.6%) of the individuals, the most common being chronic cough (observed in 30.3%). When the GOLD criterion for airway obstruction was applied, 42 (17.4%) of the individuals were classified as having COPD, compared with 23 (9.5%) when the

LLN criterion was applied (Table 1). The characteristics of the individuals, by category, are detailed in Table 1, and Figure 1 shows the prevalence of COPD by age and sex.

The overall agreement between the GOLD and LLN criteria to define obstruction was good (κ = 0.67), although there was only moderate agreement among the individuals over 70 years of age (κ = 0.42). As can be seen in Table 2, none of the individuals evaluated fit into the GOLD−/LLN+ category (post-bronchodilator FEV_1/FVC ratio < LLN and ≥ 70%). When comparing the three remaining categories, we found that the individuals in the GOLD+/LLN− category were significantly older than were those in the GOLD−/LLN− category ($p < 0.001$), although we found no significant difference in age between the two concordant categories (GOLD−/LLN− and GOLD+/LLN+; $p = 0.102$). The proportion of obese patients was lowest in the GOLD+/LLN+ category.

Individuals in the GOLD−/LLN− category had fewer symptoms than did those in the other categories. We found no differences between the GOLD+/LLN− and GOLD+/LLN+ categories in terms of presence of symptoms. The proportion of patients with dyspnea (mMRC score ≥ 2) was higher in the GOLD+/LLN− category than in the GOLD+/LLN+ category, although the difference was not statistically significant, and the two categories were comparable in terms of other COPD symptoms (Table 1).

The median DL_{CO} value was lower in the GOLD+/LLN+ category than in the GOLD−/LLN− and GOLD+/LLN− categories ($p < 0.001$ and $p = 0.038$, respectively). We found no statistically significant difference in DL_{CO} between the GOLD−/LLN− category and the GOLD+/LLN− category.

DISCUSSION

In the present study, we evaluated two different criteria to define airway obstruction in a sample of individuals with risk factors for COPD. The overall prevalence of COPD was higher when the GOLD criterion was applied than when the LLN criterion was applied (17.4% vs. 9.5%), and the concordance between the two criteria was good, albeit weaker in older individuals. The proportion of obese individuals was higher in the category that was discordant for obstruction (GOLD+/LLN−) than in the category that was concordant for obstruction (GOLD+/LLN+). The DL_{CO} was preserved in the GOLD+/LLN− (discordant for obstruction) category and in the GOLD−/LLN− (concordant for no obstruction) category. Although the individuals in the GOLD+/LLN− category were older than were those in the GOLD−/LLN− category, there was no significant difference in age between the GOLD+/LLN+ category and the GOLD−/LLN− category.

The reported prevalence of COPD varies widely because of differences in survey design, diagnostic criteria, and analytical approaches, which complicate comparisons of the data. In comparison with the findings of another study conducted in the same region of Portugal, which used the Burden of Obstructive Lung Disease protocol/GOLD criteria,[12] the prevalence of COPD was higher in the present study (14.2% vs. 17.4%). That discrepancy could be explained by the differences between the two samples. In the present study, we included only current or former smokers with risk factors for COPD who were referred for pulmonary function testing. Most other studies of this type, including the Burden of Obstructive Lung Disease study,[12] have been population-based studies.[8,10,18]

The LLN values are dependent on the chosen reference equation. Therefore, the reported prevalence of COPD is also broad, ranging from 8.2% to 14.0%, depending on the LLN used in order to define airway obstruction[19]: 8.2% when the European Community for Steel and Coal prediction equation[2] is used; 8.6% when the GLI equation is used; 10.0% when the National Health and Nutrition Examination Survey equation is used; and 14.0% when the Copenhagen City Heart Study/Copenhagen General Population Study equation is used. Among elderly individuals, the rate of airway obstruction obtained is lower when the GLI 2012 reference equation is used[16] than when those of the National Health and Nutrition Examination Survey III[3] and the European Community for Steel and Coal prediction equation[2] are used.

In the present study, the number of individuals diagnosed with airway obstruction was higher when we used a fixed criterion for evaluating the post-bronchodilator FEV_1/FVC ratio than when we used the LLN-based criterion, a finding that is consistent with those of other studies.[7,8,18,20] The GOLD criterion may overestimate airway obstruction in older individuals and underestimate it in younger individuals.[5] As in other studies,[7,12,18] the prevalence of airway obstruction evaluated with the fixed criterion increased with age in our study. However, as was also found in our study, that difference is less pronounced when the LLN criterion is used.[7] We documented good agreement between the two criteria, although the level of that agreement decreased with age, as has previously been reported.[21]

It is unknown what the most appropriate criterion to define obstruction in the diagnosis of COPD is, as well as the clinical meaning of a discordant classification. Because there is no gold-standard criterion, it is impossible to determine which criterion is better. The overdiagnosis in older individuals when the fixed criterion is used can be associated with unnecessary treatments, increased healthcare costs, adverse health effects, and failure to investigate other possible reasons for the complaints.[4] In one systematic review,[22] both criteria appeared to be associated with various clinically relevant outcomes and there were no data to justify a preference for one criterion over the other.

In regard to lung function, we found that the DL_{CO} was lower in the concordant for obstruction category than in the discordant for obstruction category, although it was comparable between the discordant for obstruction category and the concordant for no obstruction category. In keeping with our data, other

Table 1. Descriptive statistics and comparison of the categories of agreement between the GOLD and lower limit of normal criteria to define airway obstruction.[a]

Variable	Total	Category			GOLD − /LLN − vs. GOLD + / LLN −	GOLD − /LLN − vs. GOLD + / LLN +	GOLD + /LLN − vs. GOLD + / LLN +
		GOLD − /LLN −	GOLD + /LLN −	GOLD + /LLN +			
	(n = 241)	(n = 199)	(n = 19)	(n = 23)	p*	p*	p*
Male	134 (55.6)	106 (53.3)	14 (73.7)	14 (60.9)	0.426	0.637	0.637
Age (years)	60 (52-68)	58 (51-66)	71 (65-76.5)	61 (57.5-69)	< 0.001	0.102	0.079
Age range (years)							
40-49	39 (16.2)	39 (19.6)	0 (0.0)	0 (0.0)	0.069	0.069	-
50-59	79 (32.8)	66 (33.2)	4 (21.1)	9 (39.1)	0.616	0.734	0.616
60-69	73 (30.3)	61 (30.6)	4 (21.1)	8 (34.8)	0.811	0.867	0.811
≥ 70	50 (20.7)	33 (16.6)	11 (57.8)	6 (26.1)	< 0.001	0.398	0.114
BMI (kg/m^2)	27 (24-31)	27 (24-32)	28 (21-31)	25 (23.5-26.5)	0.914	0.015	0.056
Obesity (BMI ≥ 30 kg/m^2)	82 (34.0)	74 (37.2)	7 (36.8)	1 (4.35)	1	0.011	0.034
Current smoking	136 (56.4)	109 (54.8)	9 (47.4)	18 (78.3)	0.705	0.119	0.119
Smoking history (pack-years)	30 (20-45)	27 (20-43)	42 (29.5-47.5)	40 (32.5-47.5)	0.042	0.011	0.717
Symptoms	105 (43.6)	75 (37.7)	13 (68.4)	17 (73.9)	0.027	0.006	0.961
Chronic cough	73 (30.3)	55 (27.6)	5 (26.3)	13 (56.5)	1	0.028	0.147
Chronic sputum	45 (18.7)	31 (15.6)	4 (21.1)	10 (43.5)	0.769	0.009	0.342
Dyspnea (mMRC score ≥ 2)	25 (10.4)	15 (7.5)	7 (36.8)	3 (13.0)	< 0.001	0.608	0.225
Recurrent respiratory infection	23 (9.5)	15 (7.5)	2 (10.5)	6 (26.1)	0.987	0.037	0.565
Wheezing	32 (13.3)	21 (10.6)	5 (26.3)	6 (26.1)	0.147	0.147	1
Pre-BD FEV_1 (% predicted)	96 (85-106)	99 (89-108)	84.0 (75.5-90.5)	80.0 (70.5-88.5)	< 0.001	< 0.001	0.613
Category			13 (68.4)	13 (56.5)			
≥ 80%	206 (85.5)	180 (90.5)	6 (31.6)	9 (39.1)	0.018	< 0.001	0.638
≥ 50% to 80%	34 (14.1)	19 (9.5)	0 (0.0)	1 (4.4)	0.018	< 0.001	0.853
≥ 30% to 50%	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-
< 30%	0 (0.0)	0 (0.0)			-	-	-
Pre-BD FVC (% predicted)	100 (92-108)	100 (92-107)	97 (85.5-105)	106 (98.5-111)	0.393	0.144	0.195
Pre-BD RV (% predicted)[†]	119 (105-129)	117 (105-126)	136 (122.5-155)	130 (106-166)	0.004	0.055	0.358
Pre-BD TLC (% predicted)[†]	109 (102-116)	109 (100-115)	113 (107.5-118.5)	115 (112-126)	0.114	0.002	0.237
DL_{CO} (% predicted)[‡]	87 (74-100)	88 (76-100.5)	81.5 (71.3-90.8)	61 (51-78.3)	0.152	< 0.001	0.038
Post-BD FEV_1/ FVC ratio < 70%	42 (17.4)	-	-	-	-	-	
Post-BD FEV_1/ FVC ratio < LLN	23 (9.5)	-	-	-	-	-	

LLN: lower limit of normal; GOLD+: FEV_1/FVC ratio < 70%; GOLD−: FEV_1/FVC ratio ≥ 70%; LLN+: FEV_1/FVC ratio < LLN; LLN−: FEV_1/FVC ratio ≥ LLN; mMRC: modified Medical Research Council (dyspnea scale); and BD: bronchodilator. [a]Values expressed as n (%) or as median (IQR). *With Benjamini-Hochberg correction. [†]n = 222 (n = 182 in GOLD−/LLN−; n = 19 in GOLD+/LLN−; and n = 21 in GOLD+/LLN+). [‡]n = 195 (n = 160 in GOLD−/LLN−; n = 18 in GOLD+/LLN−; and n = 17 in GOLD+/LLN+).

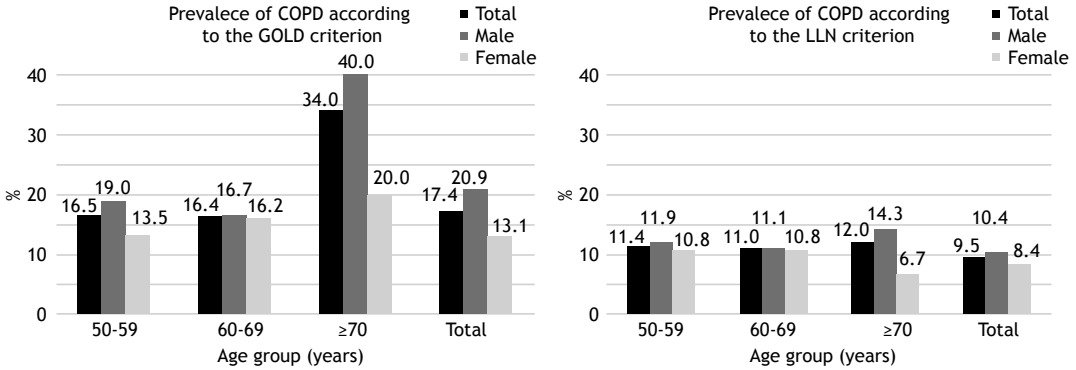

Figure 1. Prevalence of COPD by sex and age group, according to the GOLD and lower limit of normal (LLN) criteria (for the post-bronchodilator FEV_1/FVC ratio) to define airway obstruction.

Table 2. Overall agreement and agreement by age group between the GOLD and lower limit of normal criteria to define airway obstruction.

Category of agreement	Overall	Age group (years)	
		< 70	≥ 70
	(n = 241)	(n = 191)	(n = 50)
GOLD−/LLN−, n (%)	199 (82.6)	166 (86.9)	33 (66.0)
GOLD+/LLN−, n (%)	19 (7.9)	8 (4.2)	11 (22.0)
GOLD+/LLN+, n (%)	23 (9.5)	17 (8.9)	6 (12.0)
GOLD−/LLN+, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Level of agreement, κ (95% CI)	0.67 (0.52-0.81)	0.79 (0.64-0.93)	0.42 (0.12-0.72)

GOLD−: FEV_1/FVC ratio ≥ 70%; LLN−: FEV_1/FVC ratio ≥ LLN; GOLD+: FEV_1/FVC ratio < 70%; LLN+: FEV_1/FVC ratio < LLN; and κ: Cohen's kappa statistic.

studies have suggested that lung function (FVC, FEV_1, and the FEV_1/FVC ratio) is more well preserved in individuals in whom an obstructive pattern is identified according to the GOLD criterion and not according to the LLN criterion,[23] and that such individuals do not show accelerated FEV_1 decline.[24] However, the individuals in our discordant for obstruction category (GOLD+/LLN−) also showed some functional characteristics of COPD (e.g., higher RV).

Dyspnea is a cardinal symptom of COPD, although it is nonspecific and could result from other conditions, including heart disease, other lung diseases, and physical deconditioning. Some authors have reported that respiratory symptoms are less common and that potentially significant comorbidities (such as heart disease) are more frequent in "discordant obstructive" cases.[25] There is evidence suggesting that other etiologies should be considered in such cases.[22]

Although we did not thoroughly access comorbidities in our sample, we found that the proportion of obese individuals was higher in the discordant for obstruction category (GOLD+/LLN−), which is in keeping with the findings of other studies that reported a higher frequency of comorbidities in individuals with discordant results for obstruction.[25] However, not all studies have detected such a difference.[26]

We were unable to analyze the second discordant for obstruction category (GOLD−/LLN+), because none of the individuals in our sample fit into that category. That is probably a consequence of the fact that we included only individuals ≥ 40 years of age, given that the GOLD criterion has been shown to underestimate airway obstruction in individuals between 20 and 44 years of age.[5] However, because the diagnosis of COPD is based on key indicators in individuals over 40 years of age and on airway obstruction confirmed by spirometry,[1] the underdiagnosis of airway obstruction in younger individuals according to the GOLD criterion might not be a significant issue.

The present study highlights the debate on how to interpret the FEV_1/FVC ratio and the meaning of discordance between different criteria to define obstruction in the COPD diagnosis. We suggest a holistic and individualized approach for patients with discordant results for obstruction,[27] who should be followed closely. Functional, clinical, and radiological aspects beyond spirometry should be considered. Individuals in the GOLD+/LLN− category in our sample had some characteristics of COPD, such as dyspnea (mMRC score ≥ 2) and higher RV. However, that category could also include some healthy elderly individuals and individuals with symptoms due to other diseases (such as obesity and cardiovascular disease). If only the GOLD criterion is applied, it is more likely that patients will undergo unnecessary treatments and that other possible reasons for the complaints will go undiagnosed. We recommend close follow-up of patients with discordant results for obstruction, because it is possible that the LLN criterion underdiagnoses COPD

or identifies only patients with more advanced COPD. There is a need for studies focusing on the subgroup of patients with FEV_1/FVC ratio discordance.

The present study has a number of strengths. We included individuals with risk factors for COPD (current or former smokers ≥ 40 years of age), thus constructing a sample of individuals at higher risk for developing smoking-related airway obstruction. Conversely, we excluded individuals with other respiratory diseases (such as asthma and bronchiectasis) or a history of lung resection, all of which can mimic the symptoms and lung function alterations of COPD, resulting in an overestimation of its prevalence. In addition, we assessed symptoms characteristic of COPD. Furthermore, we used the GLI 2012 reference equations, which provide a robust reference standard.[16] Moreover, bronchodilator reversibility testing was performed in all individuals with airway obstruction on spirometry, whereas most studies of this topic have not included post-bronchodilator assessments or have been population-based studies that included high proportions of individuals without risk factors for COPD (asymptomatic individuals and nonsmokers) and also did not include post-bronchodilator assessments.

Our study has some limitations. We did not have access to data about exposure to harmful agents other than tobacco smoke, such as airborne pollutants (from household fuel burning, occupational sources, and ambient sources), about socioeconomic status, or about comorbidities. In addition, bronchodilator reversibility testing was performed only in subjects with pre-bronchodilator obstruction (FEV_1/FVC ratio < 70% or < LLN). However, that may not have made a significant difference, given that only a small proportion (3%) of individuals show obstruction in the post-bronchodilator evaluation after showing no airway obstruction in the pre-bronchodilator evaluation,[28] as well as that pre- and post-bronchodilator airway obstruction have been found to predict mortality with a similar degree of accuracy.[29] Furthermore, because our sample size was calculated to assess the prevalence of COPD, the number of individuals in the discordant for obstruction category was small. Moreover, we did not assess the relationship between airway obstruction on spirometry and other COPD outcomes, because we had no access to follow-up data. Finally, the reference values of the GLI 2012 equations were not applied for body plethysmography (which was not evaluable at the beginning of the data collection).

In this study, we assessed two different criteria to define airway obstruction for the diagnosis of COPD in a sample of individuals with risk factors for the disease. We documented a higher prevalence of airway obstruction when the GOLD criterion was applied than when the LLN criterion was applied (17.4% vs. 9.5%). The overall level of agreement between the two criteria was good, although it was lower in the older subjects. The use of different criteria to define airway obstruction seems to identify individuals with different characteristics. It is essential to understand the clinical meaning of discordance between such criteria. Until more data are available, we recommend a holistic, individualized approach to, as well as close follow-up of, patients with discordant results for airway obstruction.

AUTHOR CONTRIBUTIONS

MG: study conception and design; data collection; and management of the systematic database. JC: statistical analysis of the data. All of the authors reviewed the literature; interpreted and discussed the results; drafted the manuscript; and read and approved the final version.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Validation of the Brazilian Portuguese version of the University of California San Diego Shortness of Breath Questionnaire in patients with interstitial lung disease

Humberto Silva[1], Leandro Cruz Mantoani[1], Camile Ludovico Zamboti[1], Wagner Florentin Aguiar[1], Andrew L. Ries[2], Aline Ferreira Lima Gonçalves[1], Thatielle Garcia da Silva[1], Marcos Ribeiro[3], Fabio Pitta[1], Carlos Augusto Camillo[1,4]

1. Laboratório de Pesquisa em Fisioterapia Pulmonar – LFIP – Departamento de Fisioterapia, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
2. School of Medicine, University of California San Diego, San Diego (CA) USA.
3. Departamento de Pneumologia, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
4. Departamento de Ciências da Reabilitação, Universidade Pitágoras-Universidade Norte do Paraná – UNOPAR – Londrina (PR) Brasil.

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ABSTRACT

Objective: To investigate the reliability, internal consistency and validity of the Brazilian Portuguese version of the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) in patients with interstitial lung disease (ILD). **Methods:** Patients with ILD completed the questionnaire at three different time points, one week apart, with the assistance of two independent assessors. Intra- and inter-rater reliability were analysed via the intraclass correlation coefficient (ICC). Internal consistency was assessed with the Cronbach's alpha coefficient. For the validity analysis, associations between variables were assessed with Spearman's or Pearson's correlation coefficient. **Results:** Thirty patients with ILD (idiopathic pulmonary fibrosis, connective tissue disease-associated pulmonary fibrosis, sarcoidosis, asbestosis or non-specific interstitial pneumonia) were included (15 men; mean age, 59 ± 10 years; DL_{CO}: 46 [33-64] % predicted). UCSD SOBQ scores showed excellent agreement and internal consistency in the intra-rater analysis (ICC: 0.93 [0.85-0.97]; Cronbach alpha: 0.95) and in the inter-rater analysis (ICC: 0.95 [0.89-0.97]; Cronbach alpha: 0.95), as well as correlating significantly with dyspnoea (as assessed by the Medical Research Council scale; r = 0.56); Medical Outcomes Study 36-item Short-Form Health Survey domains bodily pain, general health, vitality and physical functioning ($-0.40 \leq r \leq -0.74$); six-minute walk distance (r = −0.38); and quadriceps muscle strength (r = −0.41). **Conclusions:** The Brazilian Portuguese version of the UCSD SOBQ is valid, is reliable and has internal consistency in patients with ILD in Brazil.

Keywords: Lung diseases, interstitial; Dyspnea; Surveys and questionnaires.

INTRODUCTION

Interstitial lung diseases (ILDs) are characterised by chronic alveolar inflammation, diffuse parenchymal lung fibrosis and, as a consequence, a deficit in gas exchange.[1-3] These impairments directly impact dyspnoea, exercise capacity, muscle function, physical activity, health-related quality of life, anxiety, depression and disease prognosis.[4-8]

Currently available medical treatments can slow down disease progression but do not appear to impact survival.[9] Consequently, measures of health status and symptom perception play an important role in assessing the effects of ILD, as well as treatment efficacy. Among the typical symptoms, dyspnoea related to activities of daily living is the most commonly reported by patients with ILD and significantly contributes to the perception of poorer health status.[10,11] Despite its prevalence and relevance, dyspnoea in patients with ILD has received little attention in clinical trials and studies exploring disease progression. This literature gap likely reflects the limited availability of information concerning dyspnoea perception in this group of patients and the absence of robust data pointing out the most valid and reliable criteria to assess their dyspnoea.

To evaluate the progression of certain respiratory diseases and the response to interventions such as rehabilitation programmes, several instruments exist, with different forms of administration, including interviews, self-report questionnaires, visual analogue scales and numeric scales.[12-14] The University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) comprehensively assesses breathlessness experienced during activities of daily living and can be used in a wide range of chronic respiratory diseases. The UCSD SOBQ has been validated for use in patients with COPD, patients with cystic fibrosis, lung transplant recipients[15] and patients with idiopathic pulmonary fibrosis (IPF).[16] Moreover, the UCSD SOBQ has been considered a valid

Correspondence to:
Carlos Augusto Camillo. Centro de Pesquisa e Pós-Graduação, Unidade Piza, Rua Marselha, 519, Parque Residencial Joaquim Toledo Piza, CEP 86041-140, Londrina, PR, Brasil.
Tel.: 55 43 3371-2490. E-mail: carlos.a.camillo@outlook.com
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instrument to assess changes in perceived dyspnoea over time in patients with IPF.[16]

Given that dyspnoea is a major symptom of ILD and generally limits activities of daily living and quality of life in these patients, it is essential to use valid tools to assess it adequately. This study aimed to investigate the reliability, internal consistency and validity of the Brazilian Portuguese version of the UCSD SOBQ in patients with different ILDs.

METHODS

Study design and procedures

This cross-sectional study was conducted at the *Universidade Estadual de Londrina*, located in the city of Londrina, Brazil, and was approved by the local institutional review board (Protocol no. 2.484.871). Patients with a diagnosis of ILD in accordance with international guidelines[1,2] were recruited from the university hospital outpatient clinic. The medical and pharmacological management of patients remained unchanged during the study period. Patients had to be clinically stable for at least four weeks before the first interview and in the interim between completing the questionnaire the first and second time, and the second and third time. Patients were excluded if they did not have enough cognitive function to complete the questionnaire, as assessed by the Mini-Mental State Examination,[17] or presented with health status changes that could interfere with the assessments.

In the initial visit, all participants underwent a comprehensive clinical assessment. Lung function assessment was performed in accordance with internationally accepted guidelines,[18-21] including whole-body plethysmography and DL_{CO} measurement with a Vmax plethysmograph (CareFusion, Hochberg, Germany). Exercise capacity was assessed by the six-minute walk test. The test was performed twice, and the highest six-minute walk distance was recorded.[22,23] Quadriceps muscle strength was assessed by the maximal voluntary isometric contraction of the dominant limb, with the use of a strain gauge sensor (EMG System do Brasil, São José dos Campos, Brazil). Participants were instructed to perform a maximal voluntary isometric contraction for six seconds, with 90° of hip and knee flexion.[24] Dyspnoea-related limitations in activities of daily living were assessed with the Medical Research Council (MRC) scale,[13] and health-related quality of life was assessed with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).[25,26] Furthermore, participants completed the UCSD SOBQ at three different time points (during the initial visit and two additional visits), with a maximum interval of 7 days between visits. This time frame is considered long enough for participants not to fully recall their previous responses and avoid significant changes in health status.[27]

Two investigators administered the questionnaire for the evaluation of intra- and inter-rater reliability. Investigator 1 applied the questionnaire in the first and third visits, whereas investigator 2 applied it during the second visit. A comparison of the UCSD SOBQ scores across the three time points was performed (i.e., inter- and intra-rater reliability). Furthermore, the convergent criterion validity of the UCSD SOBQ was assessed via its correlations with anchors (i.e., the MRC scale and the SF-36).

Questionnaires

Approval to use the UCSD SOBQ was obtained from the original author and from the Mapi Research Trust (Request no. 89588), which had translated the original questionnaire to Portuguese and adapted it for use in Brazil. Therefore, the translation and cross-cultural adaptation of the UCSD SOBQ was out of the scope of the present study.

The UCSD SOBQ[15] is a 21-item questionnaire that evaluates dyspnoea during activities of daily living of varying intensity (e.g., brushing one's teeth and walking uphill). Participants were asked to indicate the perceived severity of breathlessness on a six-point scale ranging from 0 (not at all) to 5 (maximal or unable to do because of breathlessness). When participants did not usually perform an activity mentioned in the UCSD SOBQ, they were instructed to estimate the degree of breathlessness to perform that activity. Three additional questions about limitations due to shortness of breath, fear of harm from overexertion and fear of shortness of breath are included for a total of 24 items. The total score ranged from 0 to 120 and was calculated by the sum of all items, in which a higher score translated to a greater limitation caused by dyspnoea.[15] The Brazilian Portuguese version of the UCSD SOBQ is available upon request to the Mapi Research Trust at https://eprovide.mapi-trust.org.

The MRC scale was used to assess dyspnoea-related limitations in activities of daily living. Scores range from 1 to 5, with higher scores indicating greater impairment.[13] The SF-36 comprises 36 questions covering eight domains of health status: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Measurements of the eight domains were transformed linearly to scores ranging from 0 (the worst possible condition) to 100 (the best possible condition).[25]

A quiet room was used for the administration of the questionnaires. Given that illiteracy is not an uncommon characteristic among Brazilians (mainly the elderly) and the considerable variation of scores when questionnaires are self-administered in comparison with when they are interviewer-administered, completion of the questionnaires at all time points in the present study was facilitated by a researcher using an interview approach.[28]

Statistical analysis

Continuous variables were described as mean ± standard deviation or median [IQR] depending on

data distribution. The intraclass correlation coefficient (ICC) was used to investigate the reliability of the questionnaire. The ICC was selected in accordance with McGraw & Wong.[29] The "two-way mixed effects, single measurement, absolute agreement" was used to investigate intra- and inter-rater agreement. Reliability was classified as poor (ICC < 0.5), moderate (0.5 ≤ ICC < 0.75), good (0.75 ≤ ICC < 0.9) or excellent (ICC ≥ 0.9).[30] Absolute reliability of the data was determined by the standard error of measurement (SEM). The SEM was calculated on the basis of intra-assessor reliability by the following equation: $SEM = SDX\sqrt{1} - ICC$. A lower SEM translated to a more reliable measurement.[31] Internal consistency was tested using Cronbach's alpha. Values ranging from 0.70 to 0.95 represent acceptable internal consistency for the instrument.[32] Agreement between tests (intra- and inter-rater agreement) was assessed by Bland-Altman analysis.[33] Ceiling and floor effects were calculated by estimating the proportion of patients whose scores lay within the 10% best UCSD SOBQ scores (ceiling effect) or the 10% worst UCSD SOBQ scores (floor effect).[34]

Spearman's correlation coefficient was used to verify correlations of UCSD SOBQ scores at all time points with other questionnaires and clinical outcomes. The MRC scale and the SF-36 were used as anchors in the validation of the UCSD SOBQ. It was hypothesized that the UCSD SOBQ would show at least moderate correlation with the MRC scale and the Physical Health component of the SF-36. The magnitude of this correlation was expected to be at least moderate (r > 0.39).[35] Statistical significance was set at p < 0.05. All statistical analyses were performed with the Statistical Analysis System, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Thirty patients were evaluated and included in the analysis. There was no attrition after inclusion. Of the 30 patients included in the analysis, 18 had IPF, 5 had connective tissue disease-associated pulmonary fibrosis, 4 had particle-induced pulmonary fibrosis, and 3 had non-specific interstitial pneumonia. The clinical characteristics of the patients are described in Table 1.

There were no differences in total UCSD SOBQ scores across the three visits (visit 1: 39 ± 23, visit 2: 42 ± 24 and visit 3: 37 ± 21; p = 0.07). As can be seen in Figure 1, the UCSD SOBQ showed excellent reliability, agreement and internal consistency on the intra-rater test-retest (visit 1 vs. visit 3; ICC: 0.93 [0.85-0.97]; Δ1.34 [95% CI: −20 to 23]; Cronbach's alpha: 0.95) and on the inter-rater test-retest (visit 1 vs. visit 2; ICC: 0.95 [0.89-0.97]; Δ−1.03 [95% CI: −22 to 20]; Cronbach's alpha: 0.95). In addition to the overall internal consistency analysis, we tested Cronbach's alpha by deleting one item at a time and obtained similar results (0.955 < α < 0.961). The proportion of patients whose scores lay within the top 10% UCSD SOBQ scores (ceiling effect), i.e., more severe shortness of breath, was = 0% (i.e., no patients). The proportion of patients whose scores lay within the bottom 10% UCSD SOBQ scores (floor effect), i.e., less severe shortness of breath, was = 3%. The SEM for the total score was 4.9 (9%) for (intra-rater) test-retest reliability.

UCSD SOBQ scores showed a moderate positive correlation with MRC scale scores (r = 0.56, p = 0.0019) and a significant negative correlation with different SF-36 domains (physical functioning, bodily pain, general health and vitality), ranging from −0.40 to −0.74 (Table 2). In addition, the UCSD SOBQ was significantly correlated with quadriceps muscle strength adjusted by body weight and the six-minute walk distance in metres (r = −0.41, p = 0.03; r = −0.38, p = 0.03, respectively). Correlations with pulmonary function variables were all non-significant (−0.12 < r < 0.25, p > 0.05 for all).

DISCUSSION

The present study results indicate that the Brazilian Portuguese version of the UCSD SOBQ has excellent internal consistency and is a reliable instrument to assess dyspnoea in patients with ILD. Furthermore,

Table 1. Clinical characteristics of the patients.

Variable	n = 30
Sex, men (%)	15 (50)
Age, years	59 ± 10
BMI, kg/m^2	27.4 ± 5.3
Pulmonary function	
FVC, % of predicted	73 [59-80]
FEV_1, % of predicted	73 [58-84]
FEV_1/FVC	84 [79-87]
TLC, % of predicted	72 [65-89]
DL_{CO}, % of predicted	46 [33-64]
Exercise capacity	
6MWD, m	469 ± 100
6MWD, % of predicted	86 ± 17
Peripheral muscle strength	
Quadriceps muscle strength, N	350 [234-530]
Quadriceps muscle strength, N/kg	5.4 [3.6-7.1]
Health-related quality of life (SF-36 domains)	
Physical functioning, score	40 [25-60]
Role-physical, score	25 [0-75]
Bodily pain, score	51 [41-62]
General health, score	47 [35-52]
Vitality, score	60 [45-70]
Role-emotional, score	67 [0-100]
Social functioning, score	74 [50-100]
Mental health, score	72 [56-76]
Dyspnoea	
MRC scale, score	3 [2-4]
UCSD SOBQ, score	37 [22-52]

6MWD: six-minute walk distance; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; MRC: Medical Research Council; and UCSD SOBQ: University of California San Diego Shortness of Breath Questionnaire.

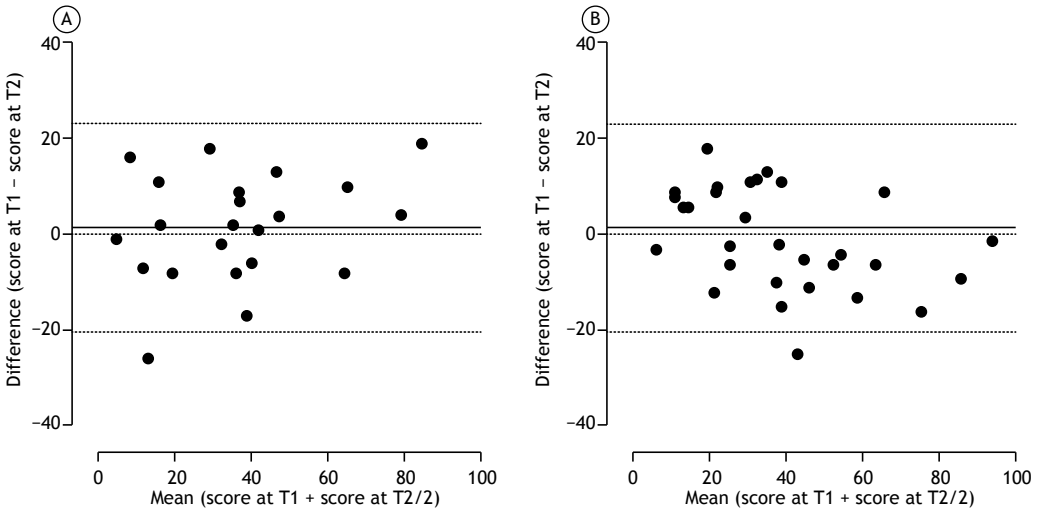

Figure 1. Bland-Altman plots showing the level of agreement between two different applications of the University of California San Diego Shortness of Breath Questionnaire (at time point 1 [T1] and time point 2 [T2]). In A, intra-rater agreement. In B, inter-rater agreement.

UCSD SOBQ scores were significantly correlated with the questionnaires used as anchors (the MRC scale and the SF-36). Moreover, the UCSD SOBQ showed good reliability and agreement when applied by the same rater and by different raters. All of these features provide a good scientific basis for using the UCSD SOBQ to assess dyspnoea in patients with ILD.

Eakin et al.[15] observed excellent internal consistency when they initially validated the UCSD SOBQ. Likewise, the values of Cronbach's alpha in the present study also showed excellent internal consistency. Importantly, neither intra-rater reliability nor inter-rater reliability was investigated in previous validation studies of the UCSD SOBQ.[15,16] Our results expand the current knowledge on the metric properties of the UCSD SOBQ, confirming excellent reliability of the UCSD SOBQ in patients with ILD. Moreover, the reliability found in the present study was excellent in both intra- and inter-rater assessments. The difference in UCSD SOBQ scores across the three evaluation time points was less than five points, which is the minimal clinically important difference for this questionnaire.[36,37] In addition, there was no statistically significant difference across the three evaluation time points ($p > 0.05$). Therefore, only one assessment is sufficient to identify the impact of dyspnoea on activities of daily living. These findings demonstrate that the UCSD SOBQ can be applied by different assessors. This facilitates its application in clinical settings such as pulmonary rehabilitation programmes.

The development study of the UCSD SOBQ[15] found a correlation with dyspnoea as assessed by modified Borg scale ratings of perceived breathlessness ($r = 0.45$) that is somewhat weaker than the correlation with the MRC scale scores found in the present study ($r = 0.56$). A likely explanation for the differences between the aforementioned results is the tool used as an anchor for dyspnoea measurements. The correlation with the MRC scale scores is possibly better because the MRC scale is designed to evaluate the degree of dyspnoea during activities of daily living, whilst the Borg scale was developed to assess dyspnoea on exertion. Since dyspnoea is strongly related to quality of life in patients with respiratory disorders, it is not surprising that previous studies have investigated associations between these two outcomes.[16,38] Interestingly, others have reported similar correlations between the UCSD SOBQ and health-related quality of life as assessed by the SF-36 (i.e., $-0.70 < r < -0.78$).[16,38] The SF-36 was chosen for the present study because it had previously been translated to Portuguese. It has been widely used in patients with ILD due to the lack of a specific questionnaire for this population.[39]

Table 2. Correlation of University of California San Diego Shortness of Breath Questionnaire scores with Medical Research Council scale and Medical Outcomes Study 36-item Short-Form Health Survey scores.

Variable	r	p
MRC scale	0.56	0.0019
SF-36 domains		
Physical functioning	−0.74	< 0.0001
Role-physical	−0.29	0.11
Bodily pain	−0.48	0.007
General health	−0.40	0.02
Vitality	−0.40	0.02
Role-emotional	−0.26	0.16
Social functioning	0.08	0.67
Mental health	−0.06	0.72

MRC: Medical Research Council; and SF-36: Medical Outcomes Study 36-item Short-Form Health Survey.

Dyspnoea is the cardinal symptom of ILD and significantly affects patient overall health status. In other respiratory diseases, dyspnoea has a negative impact on the performance of physical activities of daily living.[40] Because the UCSD SOBQ is an instrument

that evaluates the impact of dyspnoea on physical activities, we also investigated the correlation of the UCSD SOBQ with other clinical outcomes. Correlation values between the UCSD SOBQ and exercise capacity in the present study were similar to those observed in the validation study.[15,16] Moreover, we also found a significant correlation between the UCSD SOBQ and muscle strength (quadriceps muscle strength) that has not been demonstrated in previous studies.

No significant correlations were found between UCSD SOBQ scores and pulmonary function ($-0.12 < r < 0.25$, $p > 0.05$ for all) in the present study. Swigris et al. investigated associations between UCSD SOBQ scores and pulmonary function and found similar results in patients with IPF.[16] On the other hand, Eakin et al. evaluated patients with different respiratory diseases (COPD patients, cystic fibrosis patients and lung transplant recipients), which differ from ILDs in terms of lung function impairment.[15,16] Although lung function impairment is associated with dyspnoea, this correlation seems to be stronger in obstructive diseases.[15,16] Yet, the severity of lung function impairment does not appear to be a decisive factor downplaying dyspnoea in ILDs.[15]

The present study has some limitations. The low prevalence of patients with ILD and the single-centre nature of the study limited participant recruitment, resulting in a somewhat limited sample size. Notably, the reliability and validity analysis results are in line with a previous validation study in patients with IPF.[16] Therefore, sample size and composition in the present study are unlikely to have compromised the reliability of the results. Furthermore, although the UCSD SOBQ was developed to be self-administered, it was interviewer-administered in the present study. This was an a priori criterion carefully used in our study because we anticipated illiterate patients, who are not uncommon in Brazil.[28] Finally, since there is considerable variation of scores when questionnaires are self-administered in comparison with when they are interviewer-administered, we attempted to reduce bias by standardising the application method.[28] Whether or not the self-administered UCSD SOBQ is also valid and reliable in patients with ILD in Brazil remains to be confirmed.

In conclusion, although the present study was conducted in a relatively small sample, the Brazilian Portuguese version of the UCSD SOBQ was found to be a valid and reliable instrument to assess dyspnoea related to activities of daily living in patients with ILD. Furthermore, our results demonstrate that different assessors can apply the questionnaire, thus facilitating its use in clinical settings such as pulmonary rehabilitation programmes.

AUTHOR CONTRIBUTIONS

HS: conception and design of the study; data acquisition, analysis, and interpretation; drafting of the manuscript; and final approval of the version to be published. LCM and CLZ: drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. WFA, AFLG and TG: data acquisition; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. ALR: substantial contribution to the study design; data acquisition and interpretation. MR: critical revision of the manuscript for important intellectual content; and final approval of the version to be published. FP: data analysis and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. CAC: conception and design of the study; data analysis and interpretation; critical revision of the manuscript for important intellectual content; final approval of the version to be published; and guarantor of the article.

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ORIGINAL ARTICLE

Mindfulness-based treatment for smoking cessation: a randomized controlled trial

Mariana Sponholz Araujo[1,2], Lucas Gabriel da Silva[3], Gabriel Monteiro Alves Pereira[3], Nanci Ferreira Pinto[4], Fábio Marcelo Costa[2], Lucas Moreira[2], Daniella Porfírio Nunes[2], Mariane Gonçalves Martynychen Canan[2], Maria Helena Santos de Oliveira[5]

1. Disciplina de Pneumologia, Departamento de Clínica Médica, Universidade Federal do Paraná, Curitiba (PR) Brasil.
2. Departamento de Cardiopneumologia, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (PR) Brasil.
3. Faculdade de Medicina, Universidade Federal do Paraná, Curitiba (PR) Brasil.
4. Núcleo de Estudos em Saúde Coletiva do Paraná, Curitiba (PR) Brasil.
5. Departamento de Bioestatística, Universidade Estadual de Maringá, Maringá (PR) Brasil.

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Study carried out in the Departamento de Cardiopneumologia, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (PR) Brasil.

ABSTRACT

Objective: To evaluate the efficacy of a mindfulness-based treatment (MBT) for smoking cessation or reduction and compare it with that of cognitive behavioral therapy (CBT). **Methods:** This was a single-center randomized controlled clinical trial including 113 patients divided into two groups: MBT (n = 54) and CBT (n = 59). The interventions comprised eight 90-min sessions. The primary outcome was smoking cessation at 16 weeks after program initiation. Secondary outcomes included reduction in the mean number of cigarettes smoked/day at 16 weeks after treatment initiation, as well as smoking cessation and reduction in the number of cigarettes smoked/day at the last program session. Participants had to attend ≥ 50% of the sessions to be included in the primary outcome analysis. An intention-to-treat analysis was also performed. **Results:** There was no difference between the groups regarding the primary outcome (30.4% in the MBT group vs. 31.6% in the CBT group, p = 0.68) or immediate abstinence rates (47.8% in the MBT group vs. 36.8% in the CBT group, p = 0.47). Both treatments were equally effective in reducing the number of cigarettes smoked/day at the last program session (a reduction of 93.33% [0-100%] in the MBT group and of 70% [33.3-100%] in the CBT group, p = 0.92) and at 16 weeks after program initiation (a reduction of 57.1% [0-100%] in the MBT group and of 70% [25-100%] in the CBT group, p = 0.49). **Conclusions:** MBT appears to be as effective as CBT for smoking cessation or reduction and can be an option for the treatment of tobacco use disorders in Brazil

(Brazilian Registry of Clinical Trials identifier: RBR-3w2scz [http://www.ensaiosclinicos.gov.br])

Keywords: Mindfulness; Smoking cessation; Tobacco use disorder; Psychotherapy, group; Meditation; Cognitive behavioral therapy.

INTRODUCTION

Cigarette smoking is the leading cause of preventable death in the world, associated with approximately 8 million annual deaths.[1] In Brazil, 9.8% of adults are current smokers,[2] and it is estimated that 428 people die every day because of smoking-related diseases.[3] In addition, smoking costs the country 56.9 billion Brazilian reals in health care and productivity loss.[3] Although the majority of smokers claim that they want to quit smoking, only 1-5% will achieve long-term cessation without professional help.[4,5]

Most currently available treatments in Brazil are based on cognitive behavioral therapy (CBT), including the smoking cessation treatment provided by the Brazilian Unified Health Care System. Pharmacotherapies can be used in association with CBT, particularly when there is a high degree of nicotine dependence. Although this strategy has yielded positive outcomes in the short term, the cessation rates tend to decrease significantly in the long term.[6]

Mindfulness is defined as the ability to pay attention to the present moment, on purpose and nonjudgmentally.[7] Mindfulness-based treatments (MBTs) were originally targeted at stress and chronic pain disorders.[8] Later, they were successfully used in the treatment of depression, anxiety,[9] eating disorders, and addictions,[10] and only recently have they been adapted for smoking cessation.[11]

MBT targeted to smoke cessation uses meditation techniques in order to increase the awareness of thoughts, feelings, and sensations, especially those related to craving. The goal is to teach participants to step out of the "automatic pilot" that leads to smoking and to cope with cravings until they no longer occur. In contrast to CBT, the focus is not on avoiding triggers, and substitutes are not used.[11]

The efficacy of MBT for smoking cessation has been shown to be similar to or, regarding long-term abstinence maintenance, even greater than that of CBT.[11-13] In addition, MBT has been shown to be associated with mood improvement, reduction in the urge to smoke, and reduction in abstinence symptoms.[14-16]

Correspondence to:
Mariana Sponholz Araujo. Rua Marechal Deodoro, 51, Galeria Ritz, CEP 80020-310, Curitiba, PR, Brasil.
Tel.: 55 41 3233-1492. E-mail: mari_sponholz@yahoo.com.br
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To our knowledge, there have been no studies evaluating MBT for smoking cessation in Brazil. The objective of the present study was to evaluate the efficacy of MBT in comparison with CBT for smoking reduction or cessation.

METHODS

This was an open, single-center, randomized controlled clinical trial conducted between May of 2019 and January of 2020 at the Federal University of Paraná *Hospital de Clínicas*, located in the city of Curitiba, Brazil. The study was approved by the local research ethics committee (Protocol no. CAAE 02984118.8.0000.0096) and registered with the Brazilian Registry of Clinical Trials (ReBEC; primary identifier: RBR-3w2scz [http://www.ensaiosclinicos.gov.br]). All participants gave written informed consent before inclusion in the study.

Sample size calculation was performed on the basis of the results of a previous study.[11] We sought to include a total of 120 participants. Given that both interventions required active participation in the sessions, we decided to divide the participants in three groups for each intervention in order to keep the groups sufficiently small (20 participants per group). Participants were recruited through television, radio, Internet, and newspaper advertisements, as well as posters and flyers offering nonpharmacological treatment for smoking cessation.

The eligibility criteria were as follows: being ≥ 18 years of age; being a current smoker with an average consumption of at least 5 cigarettes per day and fewer than 3 months of abstinence in the past year; and being motivated to quit smoking within the next 30 days. The exclusion criteria were as follows: active substance dependence, including alcohol dependence; schizophrenia or panic disorder, diagnosed in accordance with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[17]; illiteracy; and use of medication for smoking cessation, including bupropion, varenicline, and nicotine in any form.

Participants were randomized to intervention (MBT) or control (CBT) after stratification based on age (≥ vs. < 40 years old), sex, cigarettes smoked/day (> vs. ≤ 20), level of education (≥ complete high school education or < complete high school education), and Fagerström Test for Nicotine Dependence (FTND) scores (≥ 6 vs. < 6).

Both interventions comprised 90-min sessions twice weekly for four weeks. MBT sessions were based on a protocol used in a previous study.[11] The sessions covered theoretical concepts including associative learning, "automatic pilot," and the understanding of thoughts as such (and not as absolute truths). Guided meditations common to several mindfulness programs were used, including the following: the body scan, loving-kindness meditation, sitting meditation, and mindfulness in daily activities. A technique to work with cravings "mindfully" (i.e., Recognize, Accept, Investigate, and Note what cravings feel like as they arise—RAIN) was also taught. Sessions were conducted by a qualified mindfulness instructor graduated from the Federal University of São Paulo Open Mind Center, located in the city of São Paulo, Brazil, a pulmonologist with experience in smoking cessation, and an undergraduate medical student. CBT was based on the Brazilian Unified Health Care System smoking cessation program,[18] also including exercises from the booklet *Passos para uma Vida Livre do Tabaco* (Steps to a Tobacco-Free Life)[19] and the American Lung Association Freedom from Smoking program.[20] The sessions were conducted by pulmonologists with experience in CBT for smoking cessation and an undergraduate medical student.

In addition to the in-person group sessions, home practice was suggested and additional materials were provided, including pamphlets, handouts, and recordings. Gradual reduction in cigarette consumption was encouraged, and the quit day was scheduled for the fourth session in both groups.

The primary outcome was smoking cessation at 16 weeks after program initiation. Secondary outcomes included reduction in the mean number of cigarettes smoked/day at 16 weeks after program initiation; smoking cessation and reduction in the mean number of cigarettes smoked/day at 4 weeks after program initiation (after the last session, i.e., immediate cessation); and correlation between attendance rates and percentage reduction in the mean number of cigarettes smoked/day.

Outcomes were assessed with standardized questionnaires administered by interviewers who were blinded to the intervention. Abstinence was confirmed by an exhaled carbon monoxide level of < 8 ppm.[21]

Only participants who attended at least 50% of the sessions were included in the primary analysis of the outcomes, because a minimum attendance rate was required for the learning process. An intention-to-treat analysis was performed, including all of the participants who attended at least the first session, as well as an analysis including only those who attended 75% of the sessions. Dropouts after randomization but before group assignment were excluded.

Participants who were lost to follow-up were considered nonabstinent. In accordance with standard practice in smoking cessation trials, a last-observation-carried-forward analysis was performed to quantify the number of cigarettes smoked/day.[22] In addition, attrition analysis was performed to assess systematic differences between participants with complete data and those lost to follow-up.

Data are reported as means ± SD for variables with normal distribution or as median (IQR) for variables with non-normal distribution. The unpaired t-test or the Mann-Whitney U test was used to compare continuous variables. Categorical variables were compared by

Fisher's exact test or the chi-square test. The paired t-test or the Wilcoxon test was used for within-patient comparisons. Spearman's correlation coefficient was used to evaluate associations between variables. Differences were considered significant if $p < 0.05$. Data were analyzed with the R software, version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Graphs and tables were created with GraphPad Prism software, version 9.2 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Two hundred volunteers were assessed for inclusion in the study. Of those, 145 were considered eligible and randomized to MBT (n = 73) or CBT (n = 72). After randomization, 28 participants were excluded because they withdrew from the study before group assignment; 2 participants were excluded because of severe psychiatric disorders not reported during the screening phase (schizophrenia and panic disorder), and 2 were excluded because they were abstinent at the beginning of the trial. In total, 113 participants were included in the intention-to-treat analysis: 54 from the MBT group and 59 from the CBT group (Figure 1).

Both groups were well matched for sex, age, level of education, number of cigarettes smoked/day, and FTND scores. In the MBT group, the number of previous cessation attempts was higher, with 59% (vs. 32% in the CBT group) having tried to quit smoking three times or more. Most of the participants had previously undergone smoking cessation treatment, and previous use of varenicline was more common in the MBT group (Table 1).

Baseline characteristics including sex, age, number of cigarettes smoked/day, and FTND scores remained similar when we evaluated the subgroup of participants with ≥ 50% attendance rates. Most (64%) of the participants were women, with a mean age of 51 ± 12 years, smoked > 20 cigarettes/day, and had a moderate degree of nicotine dependence (an FTND score of 5.3). There was a difference between the groups regarding the level of education ($p = 0.037$), the proportion of participants who had a college degree being higher in the MBT group than in the CBT group (65% vs. 34%; Table 2). Unlike what was observed in the intention-to-treat analysis, there were no differences between the groups regarding previous attempts to quit smoking and previous use of pharmacotherapy. In the MBT group, participants with attendance rates < 50% smoked more cigarettes/day before the study (17.8 ± 9 vs. 24.2 ± 11.8, $p = 0.03$) and had higher FTND scores (6.4 ± 2.4 vs. 5 ± 1.8, $p > 0.001$).

There were no significant differences between participants who were lost to follow-up and those with complete data regarding baseline characteristics. There was no difference between the groups regarding the primary outcome (smoking cessation at 16 weeks after program initiation) or immediate cessation rates (Figure 2).

Both treatments were effective ($p < 0.001$) in reducing the absolute number of cigarettes smoked/day at the end of treatment (a reduction of 19 cigarettes in the MBT group and of 15.5 cigarettes in the CBT group) and at 16 weeks after program initiation (a reduction of 14 cigarettes in the MBT group and of 10 cigarettes in the CBT group). There was no difference between the groups regarding this outcome (Figure 3). The relative reduction in the number of cigarettes smoked/day was = 93.3% (0-100%) in the MBT group vs. 70% (33.3-100%) in the CBT group at the end of treatment ($p = 0.92$) and 57.1% (0-100%) in the MBT group vs. 70% (25-100%) in the CBT group at 16 weeks after program initiation ($p = 0.49$).

In the intention-to-treat analysis, there were no differences between the groups regarding abstinence at 16 weeks after program initiation (12.9% in the MBT group vs. 20.3% in the CBT group, $p = 0.29$) and at the end of treatment (20.4% in the MBT group vs. 23.7% in the CBT group, $p = 0.66$). However, when we analyzed participants with ≥ 50% attendance rates, both therapies were found to be more effective.

When we evaluated the participants who completed 75% of the programs (13 participants in the MBT group vs. 14 participants in the CBT group), cessation rates were found to be higher in both groups. The cessation rate was = 69% in the MBT group vs. 43% in the CBT group ($p = 0.32$) at the end of treatment and 38% in the MBT group vs. 43% in the CBT group ($p = 0.85$) at 16 weeks after program initiation.

There was a strong correlation between attendance at the sessions and the reduction in the proportion of cigarettes smoked/day at the last program session and at 16 weeks after program initiation (Figure 4).

DISCUSSION

To our knowledge, this is the first randomized clinical trial evaluating the efficacy of MBT in comparison with CBT in Brazil. This is also the first study to adapt an MBT protocol for smoking cessation in our country. The main findings of the study are as follows: 1. no significant differences between the groups regarding abstinence rates at the end of the programs and at 16 weeks after program initiation; 2. no significant differences between the groups regarding the reduction in cigarettes smoked/day at the end of the programs and at 16 weeks after program initiation; 3. treatment efficacy comparable to that reported in the literature for both treatments and the evaluated outcomes; and 4. a strong correlation between session attendance rates and reduction in cigarettes smoked/day.

Long-term abstinence rates of approximately 16% have been achieved with the use of CBT alone (i.e., without any medication).[4] In Brazil, there is a lack of studies with adequate methodology evaluating CBT as a stand-alone treatment for smoking cessation.

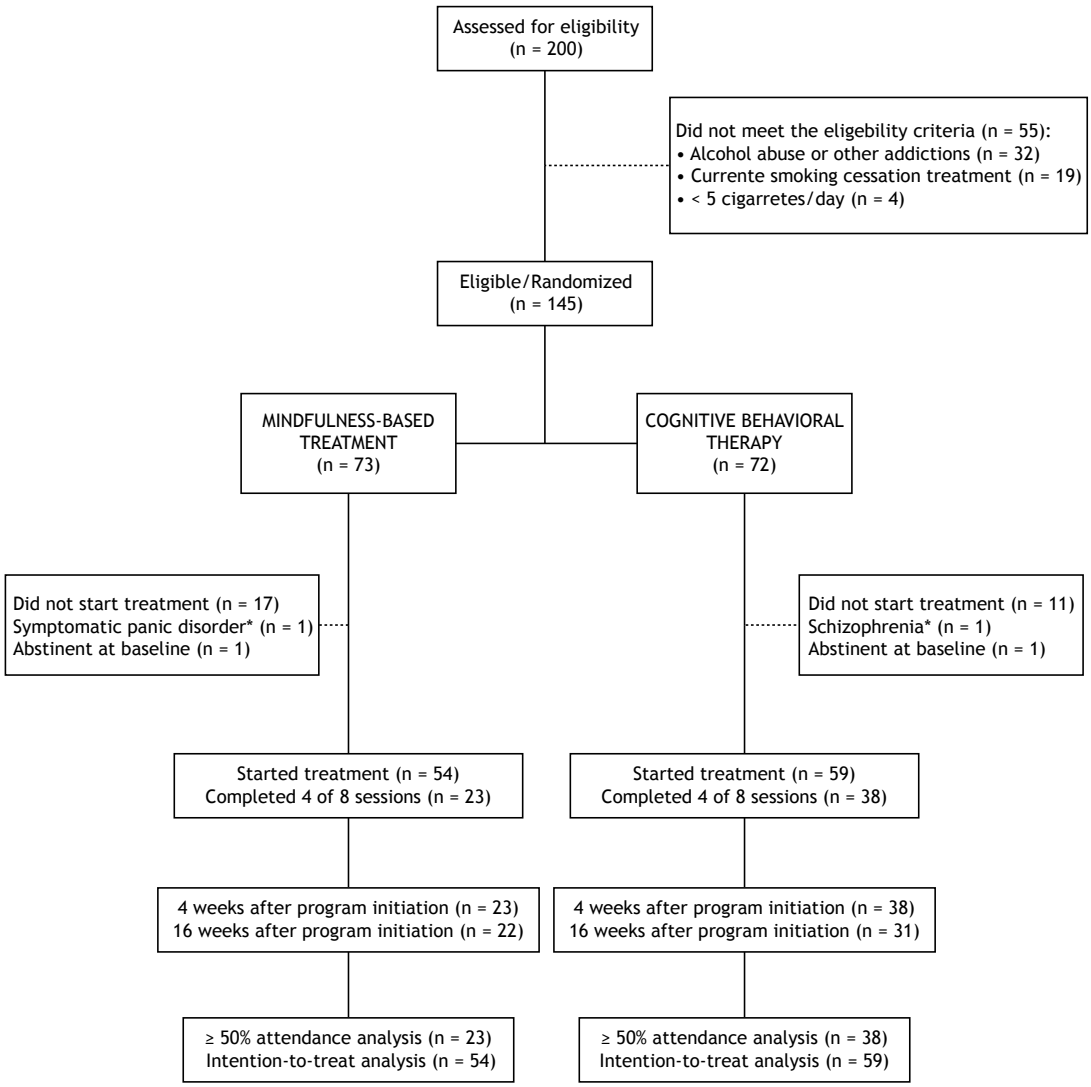

Figure 1. Flow chart of patient recruitment, enrollment, and follow-up. *Not reported at screening.

The available studies are small, are not randomized studies, are retrospective in nature, lack an objective verification of abstinence, or any combination of the four. Nevertheless, we chose to use CBT as a control intervention for several reasons: 1) It is the standard of care in our country; 2) It has demonstrated efficacy in epidemiological studies[23]; 3) It has standardized materials; 4) Pulmonologists in Brazil are trained in administering CBT; and 5) The components of CBT are well matched to those of MBT, although the methods proposed for achieving cessation are different.

In a 2013 epidemiological study of CBT-based smoking cessation programs in the state of Paraná, Brazil,[23] 54% of the study participants attended the fourth (and last) treatment session; of those, 41% claimed to be abstinent (although this was not objectively determined). In addition, 61% were also receiving pharmacological treatment for smoking cessation.[23] In the present study, the MBT group achieved an abstinence rate of 20.4% at the end of the program in the intention-to-treat analysis and an abstinence rate of 47.8% when only participants with ≥ 50% attendance rates were evaluated. These results are comparable to those in the literature and are similar to those in the control group in our study.

In the present study, immediate cessation rates were = 47.8% in the MBT group and 36.8% in the CBT group (p = 0.25), whereas, in the study on which our MBT protocol was based, immediate cessation rates were = 36% in the MBT group and 15% in the CBT group (p = 0.063).[11] With regard to long-term abstinence, cessation rates were = 30.4% in the MBT group and 31.6% in the CBT group (p = 0.68) in the present study, whereas, in the aforementioned study, they were = 31% in the MBT group and 6% in the CBT group (p = 0.012).[11] Therefore, the results were comparable between the two MBT groups, whereas the CBT group in the present study performed better

Table 1. Participant baseline characteristics, by treatment group.[a]

Characteristic	Overall sample (n = 113)	MBT (n = 54)	CBT (n = 59)	p
Sex				0.85
Female	69 (61.1)	32 (59.3)	37 (62.7)	
Male	44 (38.9)	22 (40.7)	22 (37.3)	
Age	50.3(11.6)	50.7(12.2)	49.9 (11.3)	0.71
Cigarettes/day	20.8 (9.2)	21.5(11.1)	20.2(7.2)	0.47
FTND score	5.7 (2.2)	5.8 (2.3)	5.7 (2.1)	0.84
Previous therapies	58 (51.3)	28 (51.8)	29 (50.8)	0.91
NRT	39 (34.5)	24 (37)	15 (32.2)	0.58
Bupropion hydrochloride	28 (24.7)	17 (24.1)	11 (25.4)	0.86
Varenicline	7 (6.1)	6 (11.1)	1 (1.7)	0.038
CBT	5 (4.4)	4 (3.7)	1 (5.1)	0.72
Level of education				0.22
< 9 years of schooling	7 (6.2)	4 (7.4)	3 (5.1)	
= 9 years of schooling	5 (4.4)	2 (3.7)	3 (5.1)	
High school (incomplete)	10 (8.8)	7 (13)	3 (5.1)	
High school (complete)	26 (23)	9 (16.7)	17 (28.8)	
College (incomplete)	16 (14.2)	5 (9.3)	11 (18.6)	
College (complete)	49 (43.4)	27 (50)	22 (37.3)	
Previous attempts to quit				0.04
None	14 (12.4)	5 (9.3)	9 (15.3)	
1 or 2	38 (33.6)	15 (27.8)	23 (39)	
3 or 4	36 (31.9)	18 (33.3)	18 (30.5)	
5 or more	18 (15.9)	14 (25.9)	4 (6.8)	
Attendance rate	3.9 (2.5)	3.6 (2.6)	4.2 (2.3)	0.2

MBT: mindfulness-based treatment; CBT: cognitive behavioral therapy; and NRT: nicotine replacement therapy. [a]Data presented as n (%).

than did that in the aforementioned study.[11] In a larger clinical trial, in which either CBT or MBT was used in association with nicotine patches, immediate cessation rates were = 42.1% in the MBT group and 39.1% in the CBT group, and long-term cessation rates were = 19.4% in the MBT group and 23.8% in the CBT group.[12] Similar to our study, no significant differences were found between the two interventions in that study.[12] However, MBT showed benefits over CBT in promoting recovery from a lapse,[12] an outcome that was not evaluated in the present study.

Adherence to the programs had a direct impact on the results. This was corroborated by a positive correlation between attendance rates and the reduction in the number of cigarettes smoked/day, as well as by higher quit rates in participants with attendance rates ≥ 50% and 75%.

The main strength of our study lies in the fact that we were able to conduct a randomized controlled clinical trial with a diverse sample of smokers, including men and women of different age groups and levels of education. Another strength lies in the fact that the groups were matched for the duration of sessions and proposed home activities. In addition, assessing abstinence with a standardized questionnaire applied by an interviewer who was blinded to the intervention and performing exhaled carbon monoxide measurements made the outcomes more reliable. We also believe that the statistical analysis based on the attendance rates led to a better understanding of the results.

Our study has limitations that need to be addressed. The high number of dropouts reduced the power of the study and did not allow a detailed subgroup analysis. Withdrawal from the study before intervention assignment was higher in the MBT group, meaning that the number of participants in the MBT group was lower from the outset. This difference was accentuated when the subgroups with a minimum attendance rate of 50% were evaluated. This can be partially explained by the fact that the number of individuals with multiple cessation attempts, previous use of antismoking drugs, or a combination of the two was higher in the MBT group, a difference that disappeared in the subgroup with attendance rates ≥ 50%. Another hypothesis is that MBT might be easier to apply in individuals with a higher level of education, given that knowledge about meditation is more widespread in this population.[24] In our study, groups were well matched for level of education in the intention-to-treat analysis. However, the MBT group showed a higher prevalence of individuals with a higher level of education when we analyzed the subgroup of patients with ≥ 50% attendance rates. In addition, dropouts were higher in MBT group individuals who smoked more and had higher

Table 2. Baseline characteristics of the participants with ≥ 50% attendance rates, by treatment group.

Characteristic	Overall sample (n = 61)	MBT (n = 23)	CBT (n = 38)	p
Gender (%)				0.22
Female	39 (63.9)	12 (52.2)	27 (71.1)	
Male	22 (36.1)	11 (47.8)	11 (28.9)	
Age	50.7 (12.3)	53.7 (13)	48.9 (11.6)	0.15
Cigarettes/day	19.5 (7.9)	17.8 (9)	20.5 (7.2)	0.23
Fargeström	5.3 (2)	5 (1.8)	5.6 (2.1)	0.24
Previous therapies (%)	37 (60.6)	13 (56.5)	24 (63.2)	0.61
NRT	23 (37.7)	10 (43.5)	13 (34.2)	0.77
BUP	18 (29.5)	6 (26.1)	12 (31.6)	0.76
Varenicline	6 (9.8)	5 (21.7)	1 (2.6)	0.06
CBT	4 (6.5)	1 (4.3)	3 (7.9)	0.95
Education (%)				0.037
Incomplete Elementary School	4 (6.6)	1 (4.3)	3 (7.9)	
Complete Elementary School	1 (1.6)	0 (0)	1 (2.6)	
Incomplete High School	4 (6.6)	3 (13)	1 (2.6)	
Complete High School	14 (22.9)	2 (8.7)	12 (31.6)	
Incomplete College	10 (16.4)	2 (8.7)	8 (21.1)	
Complete College	28 (45.9)	15 (65.2)	13 (34.2)	
Previous attempts (%)				0.1
None	8 (13.1)	2 (8.7)	6 (15.8)	
1 or 2	21 (34.4)	5 (21.7)	16 (42.1)	
3 or 4	23 (37.7)	11 (47.8)	12 (31.6)	
5 or more	7 (11.4)	5 (21.7)	2 (5.3)	
Attendances	5.7 (1.7)	6.2 (1.7)	5.4 (1.7)	0.07

MBT: mindfulnes-based treatment; CBT: cognitive behavioral therapy; NRP: nicotine replacement therapy; and BUP: bupropion hydrochloride.

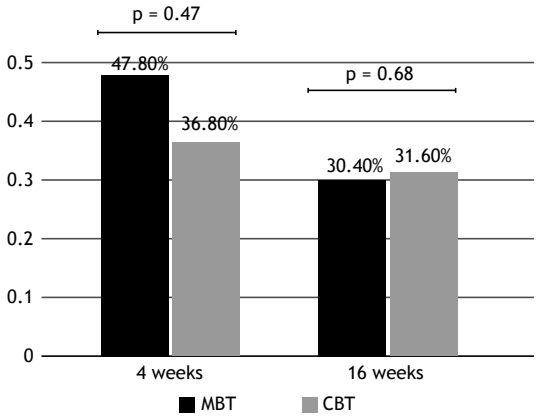

Figure 2. Abstinence rates by treatment group at 4 weeks after program initiation and at 16 weeks after program initiation (subgroup of patients with ≥ 50% attendance rates). MBT: mindfulness-based treatment; and CBT: cognitive behavioral therapy.

FTND scores, situations in which the association of pharmacotherapy is usually recommended.[25]

Missing data rates as a result of loss to follow-up in the long term were higher in the CBT group than in the MBT group (18% vs. 4%). Given that recurrence is common in this scenario, we believe that using the last-observation-carried-forward analysis might have underestimated the number of cigarettes consumed by some of those participants, therefore favoring the CBT group.

Another potential limitation is that the MBT instructors had little experience with the therapy applied. Although we had a certified mindfulness instructor and a pulmonologist with experience in smoking cessation, this was our first experience implementing a mindfulness-based protocol for smoking cessation. Professionals with more experience and maintenance sessions might have achieved even greater results.

In conclusion, the results of the present study indicate that MBT is as effective as CBT in promoting smoking cessation or reduction. If we consider that nicotine dependence is a very difficult-to-treat disease affecting millions of people of different socioeconomic, educational, and cultural backgrounds, we can understand how important it is to have different treatment options. Because MBT uses a strategy that is significantly different from CBT, it might become an interesting alternative, especially in individuals who have been unable to quit by using standard treatment.

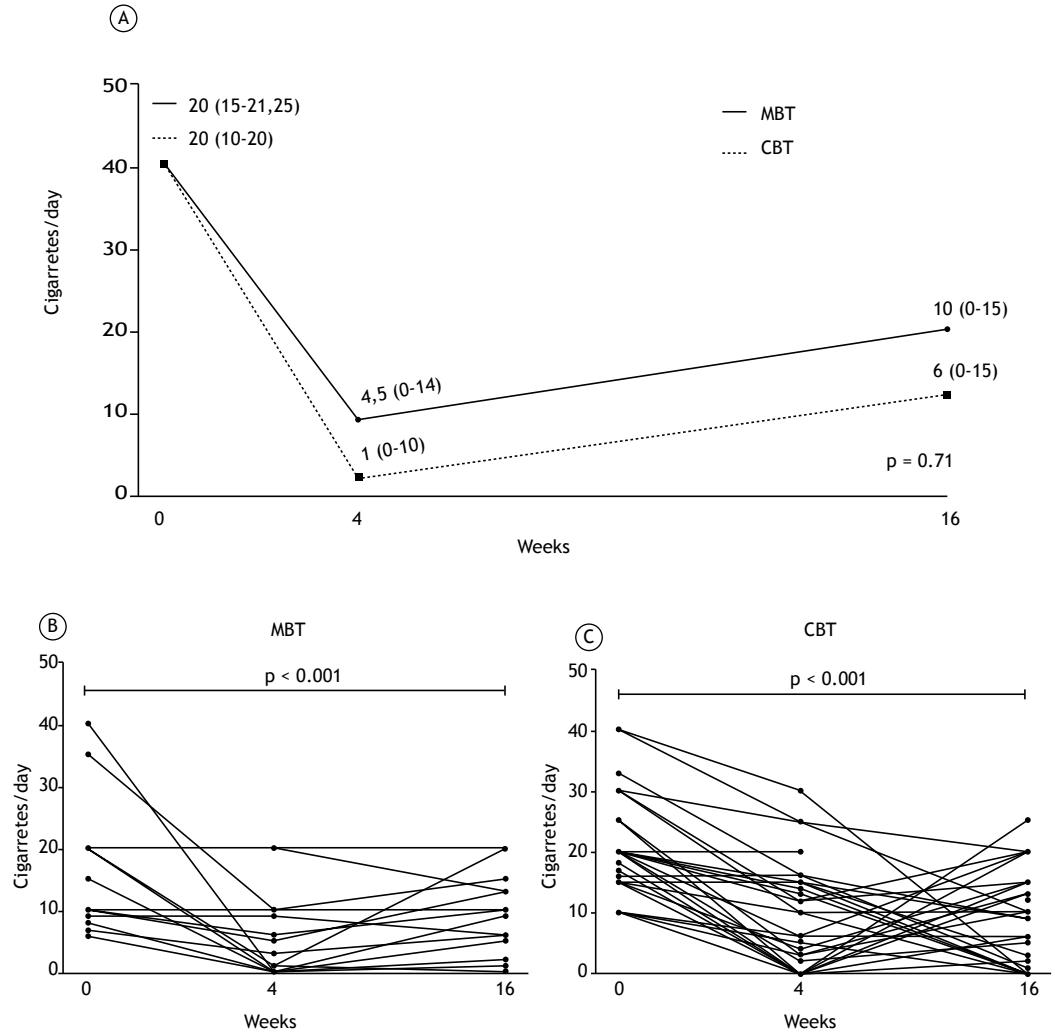

Figure 3. Smoking reduction at the end of mindfulness-based treatment (MBT) or cognitive behavioral therapy (CBT). In A, median number of cigarettes smoked/day in the MBT and CBT groups at 4 weeks after program initiation and at 16 weeks after program initiation. In B, variation in the number of cigarettes smoked/day for each participant in the MBT group (n = 23). In C, variation in the number of cigarettes smoked/day for each participant in the CBT group (n = 38).

Multicenter studies with larger samples are warranted to understand fully the potential of MBT for smoking cessation. Such studies will also be important in identifying the subsets of patients who will most likely benefit from this intervention, as well as in investigating the use of MBT in association with pharmacotherapy.

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AUTHOR CONTRIBUTIONS

MSA, LGS, and GMAP: conception and planning of the study; interpretation of evidence; drafting and revision of preliminary and final versions; and approval of the final version. NFP: conception and planning of the study; drafting and revision of preliminary and final versions; and approval of the final version. FMC, LM, DPN, and MC: planning of the study; revision of the final version; and approval of the final version. MHSO: interpretation of evidence; revision of the final version; and approval of the final version.

CONFLICT OF INTEREST

None declared.

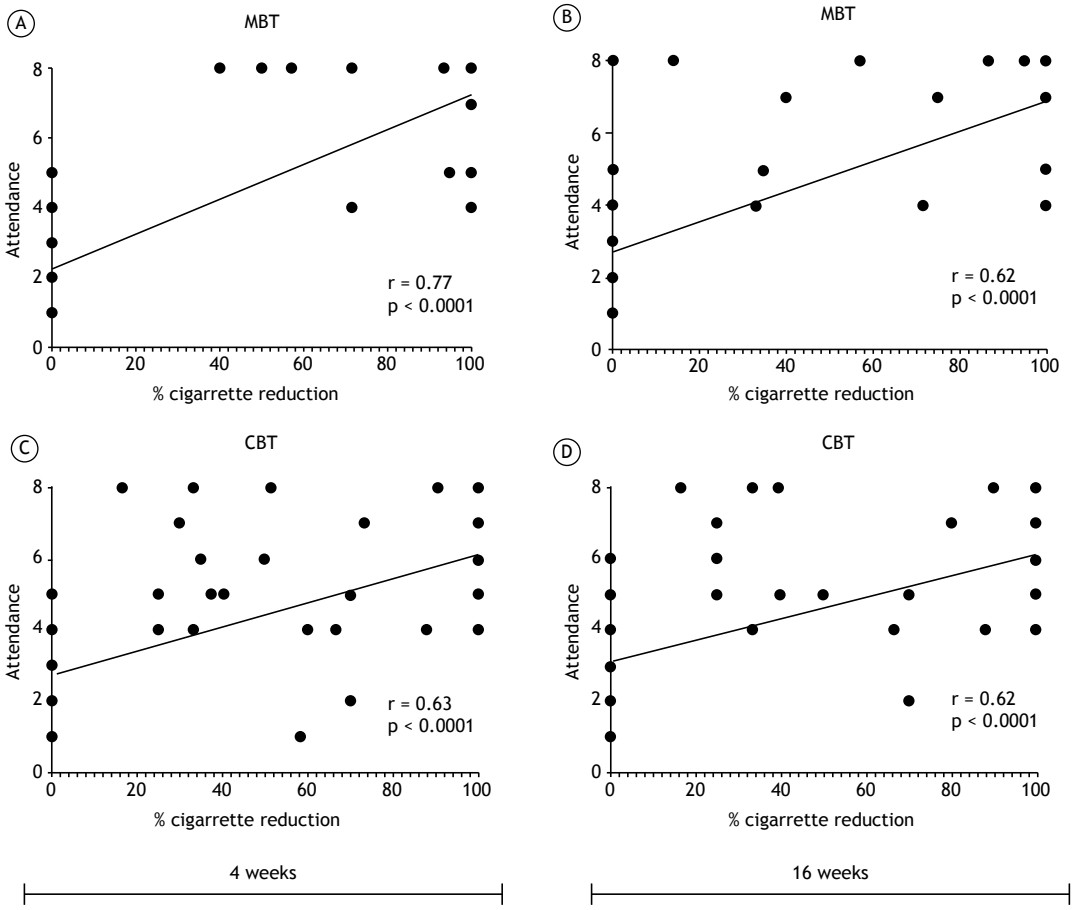

Figure 4. Correlation between smoking cessation program attendance and the percentage of reduction in the number of cigarettes smoked/day at 4 weeks after program initiation (in A and C) and at 16 weeks after program initiation (in B and D) in the mindfulness-based treatment (MBT) group and in the cognitive behavioral therapy (CBT) group.

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2021 Brazilian Thoracic Association recommendations for the management of severe asthma

Regina Maria de Carvalho-Pinto[1], José Eduardo Delfini Cançado[2], Marcia Margaret Menezes Pizzichini[3], Jussara Fiterman[4], Adalberto Sperb Rubin[5,6], Alcindo Cerci Neto[7,8], Álvaro Augusto Cruz[9,10], Ana Luisa Godoy Fernandes[11], Ana Maria Silva Araujo[12], Daniela Cavalet Blanco[13], Gediel Cordeiro Junior[14,15], Lilian Serrasqueiro Ballini Caetano[11], Marcelo Fouad Rabahi[16], Marcelo Bezerra de Menezes[17], Maria Alenita de Oliveira[18], Marina Andrade Lima[19], Paulo Márcio Pitrez[20]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Faculdade de Ciências Médicas, Santa Casa de Misericórdia de São Paulo, São Paulo (SP) Brasil.
3. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
4. Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
5. Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA – Porto Alegre (RS) Brasil.
6. Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.
7. Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
8. Pontifícia Universidade Católica do Paraná – PUCPR – Londrina (PR) Brasil.
9. Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
10. Fundação ProAR, Salvador (BA) Brasil.
11. Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
12. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro – IDT/UFRJ – Rio de Janeiro (RJ) Brasil.
13. Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS), Brasil.
14. Hospital Júlia Kubitschek, Fundação Hospitalar do Estado de Minas Gerais – FHEMIG – Belo Horizonte (MG) Brasil.
15. Hospital Madre Teresa, Belo Horizonte (MG) Brasil.
16. Faculdade de Medicina, Universidade Federal de Goiás – UFG – Goiânia (GO) Brasil.
17. Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP) Brasil.
18. Universidade Federal da Paraíba – UFPB – João Pessoa (PB) Brasil.
19. Hospital Dia do Pulmão, Blumenau (SC) Brasil.
20. Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.

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ABSTRACT

Advances in the understanding that severe asthma is a complex and heterogeneous disease and in the knowledge of the pathophysiology of asthma, with the identification of different phenotypes and endotypes, have allowed new approaches for the diagnosis and characterization of the disease and have resulted in relevant changes in pharmacological management. In this context, the definition of severe asthma has been established, being differentiated from difficult-to-control asthma. These recommendations address this topic and review advances in phenotyping, use of biomarkers, and new treatments for severe asthma. Emphasis is given to topics regarding personalized management of the patient and selection of biologicals, as well as the importance of evaluating the response to treatment. These recommendations apply to adults and children with severe asthma and are targeted at physicians involved in asthma treatment. A panel of 17 Brazilian pulmonologists was invited to review recent evidence on the diagnosis and management of severe asthma, adapting it to the Brazilian reality. Each of the experts was responsible for reviewing a topic or question relevant to the topic. In a second phase, four experts discussed and structured the texts produced, and, in the last phase, all experts reviewed and approved the present manuscript and its recommendations.

Keywords: Asthma/therapy; Asthma/drug therapy; Asthma/prevention & control; Antibodies, monoclonal, humanized.

INTRODUCTION

Advances in the understanding of the pathophysiology and heterogeneity of severe asthma have led to new approaches to diagnosis and characterization of severe asthma, as well as to new effective drugs for asthma control. These are promising times for the management of severe asthma, which, despite being an uncommon presentation of asthma, has a major impact on the health care system and on patients' quality of life.

Increasing knowledge of cellular, molecular, and genetic mechanisms involved in the pathophysiology of asthma has led to advances in the characterization of phenotypes and endotypes, as well as in the personalized management of asthma.[1]

Given the heterogeneity and complexity of severe asthma, case identification requires specialist follow-up, preferably at a referral center. Systematized approach and follow-up are needed in order to confirm the diagnosis; gather evidence of treatment adherence; ensure correct inhaler use; investigate and control comorbidities; and optimize pharmacological and nonpharmacological interventions.[2-4]

Previous estimates of disease prevalence and cost have been based on older definitions that are no longer current used,[5] resulting in overestimated prevalence. More recently, a study conducted in the Netherlands and using the American Thoracic Society/European Respiratory Society (ATS/ERS) definition of severe asthma,[3] 3.7% of asthma patients were estimated to have severe asthma.[6] In a database

Correspondence to:
Regina Maria de Carvalho-Pinto. Avenida Enéas de Carvalho Aguiar, 44, Cerqueira César, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5191. E-mail: regina.carvalho@incor.usp.br
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analysis conducted in the United Kingdom in 2018, < 1% of asthma patients were estimated to have uncontrolled severe eosinophilic asthma.[7]

Patients with severe asthma have increased morbidity and mortality,[8] a greater number (and increasingly severe) of comorbidities,[9] and more frequent health care utilization for asthma.[10] Severe asthma has been shown to result in very high costs to families and to the Brazilian Unified Health Care System.[11] An intervention implemented at an asthma referral center in Brazil and involving the provision of free medication was found to be effective in improving disease control and reducing associated costs.[12] In a study analyzing a database from the Brazilian private health care system between 2010 and 2015, the mean cost per hospitalization for asthma was shown to be $8,655.00 (in U.S. dollars).[13] Therefore, the cost of not providing access to experienced specialists at referral centers or personalized treatment alternatives for specific asthma phenotypes can be very high.

The present recommendations provide physicians with guidance on the management of severe asthma in adults, adolescents, and children ≥ 6 years of age. A total of 17 pulmonologists from referral centers for severe asthma in Brazil were invited to review the current knowledge of severe asthma and develop these recommendations adapted for Brazil. An expert panel examined major advances in topics such as the definition of severe asthma, phenotyping, biomarkers, and new treatments for severe asthma. On the basis of current evidence and international guidelines, each panel member was assigned a topic for review. Harmonization was performed in two phases. In the first phase, 4 panel members discussed and structured all texts. In the second phase, all panel members reviewed, discussed, and revised the recommendations until a consensus was reached.

DEFINITION OF SEVERE ASTHMA

Severe asthma is a subset of difficult-to-control asthma (DCA). DCA is asthma that remains uncontrolled despite step IV or V treatment[2,14] or that requires step IV or V treatment because of the concomitant presence of one or more factors affecting disease control. Potentially modifiable or controllable factors are responsible for the difficulty in achieving and maintaining disease control.

This document defines as having severe asthma the patient with asthma confirmed by an objective method, with good adherence to treatment, and who, despite the elimination or minimization of factors associated with lack of disease control, requires high doses of inhaled corticosteroids (IC; (budesonide ≥ 1600 µg or equivalent) associated with a second controller drug (long-acting beta2 bronchodilator - LABAs and/or long-acting antimuscarinic - LAMAs and/or antileukotrienes) or oral corticosteroids (OC) ≥ 50% of the days of previous year, to maintain control of the disease or that it still remains uncontrolled, due to the intrinsic severity of the asthma.[3]

DIAGNOSTIC INVESTIGATION OF DCA AND SEVERE ASTHMA IN ADULTS

Confirmation of asthma diagnosis

The diagnostic investigation of DCA and severe asthma begins with an objective confirmation of the diagnosis because, given the complexity of diagnosing asthma, misdiagnosis is common and results in inappropriate management.[15] Asthma is characterized by respiratory symptoms, variable airflow limitation, and airway hyperresponsiveness.[14] An FEV_1/FVC ratio below the lower limit of normal constitutes evidence of obstructive lung disease on spirometry. Airflow obstruction reversibility is evidenced by an acute (10-15 min) FEV_1 response to a short-acting inhaled bronchodilator (albuterol, 200-400 µg). A significant bronchodilator response is defined as a ≥ 12% and ≥ 200 mL increase in FEV_1 from baseline[16] or a ≥ 7% and ≥ 200 mL increase in FEV_1 over the reference values.[17] Airflow obstruction reversibility is also demonstrated by comparing baseline lung function and lung function parameters after 4 weeks of treatment with corticosteroids or by comparing lung function parameters between visits during periods of clinical stability.[18,19] Daily PEF variability > 20% can also be helpful in confirming the diagnosis of asthma.[4]

Changes in bronchodilator response are also evidenced by an increase in FVC, a ≥ 350 mL increase being considered significant.[17] This most commonly occurs in the presence of severe obstruction as a consequence of hyperinflation, air trapping, or both.[20]

The absence of bronchodilator response on spirometry does not exclude a diagnosis of asthma, particularly in severe asthma, which can present with airway remodeling, increased airflow obstruction, and reduced FEV_1.[21] In such cases, when spirometry fails to characterize asthma, other diagnostic methods can be used. Spirometry can be repeated after appropriate washout from bronchodilators[22] during the onset of symptoms, or after a course of systemic corticosteroids showing a > 10% change in FEV_1.[23]

Another diagnostic option is methacholine challenge testing.[24] Corticosteroid treatment reduces bronchial hyperresponsiveness (BHR); therefore, negative challenge testing in patients treated with corticosteroids does not exclude a diagnosis of asthma.[24,25] In addition, corticosteroid treatment can be gradually tapered in clinically stable patients with negative challenge testing, a 2- to 4-week follow-up period being followed by another functional assessment.

In patients with severe asthma, lung function can be assessed with plethysmography by measuring lung volumes,[3,4] adding parameters that express airflow obstruction such as lung hyperinflation and air trapping. Plethysmography can also be used in order to demonstrate airflow obstruction reversibility

by showing significant reductions in RV and specific airway resistance after bronchodilator administration.[26]

Although small airway changes can be present in patients with asthma regardless of asthma severity, they are more common in those with disease that is more severe.[27] Tests such as impulse oscillometry, nitrogen washout, plethysmography, spirometry, or any combination of the four can contribute to the identification of small airway dysfunction. $FEF_{25-75\%}$ and CVF reduction have been found to be the physiological parameters that best reflect small and medium airflow obstruction.[27] Small airway dysfunction must be carefully evaluated in patients with severe asthma because it can increase the difficulty in achieving disease control.

In the diagnostic investigation of severe asthma, HRCT is recommended[4] for making a differential diagnosis and investigating respiratory comorbidities. In addition, HRCT can help characterize small airway involvement, air trapping, airway narrowing, bronchial wall thickening, and mucus plugging, all of which are associated with increased asthma severity.[28] Dynamic HRCT (including neck imaging) can be used in order to evaluate vocal cord dysfunction and excessive central airway collapse (tracheobronchomalacia, dynamic airway collapse, or both).[29]

Assessment of treatment adherence and inhaler technique

Treatment adherence is associated with patient level of education, beliefs, and access to medication and health care.[30] There is no relationship between poor adherence to asthma controller medications and the severity of asthma.[31] In patients with DCA, adherence to inhaled controller medications is approximately 50%,[32,33] even in specialized severe asthma centers.[34] Assessing treatment adherence in clinical practice is challenging because the instruments that are currently available still need improvement.[35]

Adherence to treatment with the ICS+LABA combination is > 80% in less than half of severe asthma patients before and after initiation of treatment with biologicals.[36-39] In addition, adherence to maintenance treatment should be constantly evaluated[36,40] because patients with good adherence to ICS respond better to treatment with biologicals.[40,41]

Inhaler technique is as important as treatment adherence, being one of the major causes of poorly controlled asthma.[34] A systematic evaluation of all inhaler technique steps is essential because of the association between some of the steps and poorly controlled asthma.[42]

Correct inhaler use requires ongoing training. Despite educational interventions, inhaler technique errors are common even in patients with severe asthma.[43] In a study in which treatment adherence and inhaler technique were simultaneously and objectively evaluated in patients with moderate-to-severe asthma, 27% achieved asthma control after improving their inhaler technique.[43]

Investigation of exposures that can worsen asthma control

Achieving and maintaining asthma control can be difficult because of exposures such as allergens, irritants, environmental pollution, smoking, occupational agents, and/or drugs. Because these exposures lead to poor asthma control, they should be addressed in all asthma patients, especially those with DCA.[4]

Household exposure

Mites, cats, dogs, cockroaches, rodents, and fungi are the urban and domestic allergens that are most commonly associated with difficulty in controlling asthma.[44,45] Although only a few population-based studies have examined the prevalence of atopy in Brazil, evidence suggests that sensitization to aeroallergens varies across regions and types of study.[46,47]

Studies examining the efficacy of measures to prevent exposure to house dust in controlling asthma[48,49] have yielded controversial results. There is no consensus among guidelines regarding the usefulness of such measures in accordance with a study carried out in 2020.[49]

Environmental exposure

There is an association between air pollution and asthma exacerbation.[50,51] Air pollutants associated with worsening asthma control include fine particulate matter ($PM_{2.5}$), ozone, nitrogen dioxide, and carbon monoxide. In 2015, ozone and $PM_{2.5}$ accounted for 8-20% and 4-9%, respectively, of asthma ER visits worldwide.[52] Special attention should be given to exposure to $PM_{2.5}$ from biomass burning, because it is associated with increased ER visits and hospitalizations for asthma.[53] In a study conducted in Brazil, there was a 50% increase in hospital admissions for asthma during the sugarcane burning season.[54]

Exposure to smoking

Active and passive smoking are associated with increased exacerbations, hospitalizations, and lung function impairment, but smoking cessation or reduction is an independent, modifiable factor for asthma control.[55] Therefore, it is important to evaluate patient smoking status at each visit in order to achieve smoking cessation.

Asthma patients who use illicit drugs are more likely to require intensive care or experience severe exacerbations, especially when illicit drug use is associated with poor adherence to asthma controller medications.[56]

Work-related exposure

Workplace exposures have major clinical implications for severe asthma. Work-related asthma (WRA) includes occupational asthma (OA) and work-exacerbated asthma (WEA), which is also known as work-aggravated asthma.

OA is defined by the presence of asthma symptoms and reversible airflow obstruction, BHR, or a combination of the two as a result of workplace exposures rather than exposures outside the workplace. It can be caused by sensitizers or irritants.[57,58] WEA is defined as preexisting asthma worsened by workplace conditions.[59]

OA and WEA are primarily triggered by inhaled fumes, gases, dust, and smoke.[60] Workers such as bakers, agricultural workers, metalworkers, carpenters, and workers exposed to latex are at an increased occupational risk, and these workplace exposures should be carefully investigated and excluded as a cause of poorly controlled asthma.[61]

The estimated incidence and prevalence of OA and WEA vary depending on the study population and workplace exposure. In an analysis of 9 studies, the estimated incidence of OA was 16%.[60] However, there is little information on the impact of occupational exposure on severe asthma.[62]

In a European cohort of patients with OA (N = 997), the prevalence of severe asthma was 16.2%. Asthma severity was correlated with persistent exposure to the causative agent, asthma duration, education level, early-onset asthma, and sputum production.[62]

In severe asthma patients suspected of having poorly controlled asthma because of workplace exposures, a diagnostic flow chart[63] should be used for diagnostic confirmation. Once the diagnosis is confirmed, patients should be removed from exposure.[63]

Identification and management of comorbidities

Identification and management of comorbidities potentially affecting asthma control is part of the multidisciplinary approach to DCA and severe asthma because comorbidities are associated with worse outcomes.[64,65] Comorbidities are, for the most part, treatable, and appropriate comorbidity management can reduce the dose and required number of asthma controller medications, contributing to improving asthma control and patient quality of life, as well as reducing asthma exacerbations.

The prevalence of comorbidities in patients with severe asthma is high (ranging from 51% to 95%).[66,67] In a study conducted in Brazil, all of the patients with severe asthma reported having at least one comorbidity, and approximately 70% reported having at least three. The most common comorbidities were rhinitis, gastroesophageal reflux disease (GERD), and hypertension.[68]

Upper airway comorbidities

Allergic rhinitis and chronic rhinosinusitis with or without nasal polyps

The prevalence of allergic rhinitis is 80% in patients with asthma.[69] In Brazil, the prevalence of allergic rhinitis in patients with severe asthma ranges from 72% to 96.5%.[68,70] A diagnosis of allergic rhinitis is made on the basis of patient clinical history and a nasal symptom questionnaire, as well as a positive aeroallergen-specific IgE screen, a positive skin prick test for aeroallergens, or both. Nearly half of patients with severe asthma have chronic rhinosinusitis with or without nasal polyps.[71,72] A diagnosis of chronic rhinosinusitis is made on the basis of patient clinical history, a nasal symptom questionnaire, sinus CT, and nasofibroscopy.

Studies have shown that appropriate management of allergic rhinitis and rhinosinusitis with or without nasal polyps has a positive impact on asthma control.[73-75]

Obstructive sleep apnea

In adults, obstructive sleep apnea (OSA) is most prevalent in patients with severe asthma and is an independent risk factor for poor asthma control,[76] being associated with more severe exacerbations[77] and accelerated decline in lung function.[78]

A diagnosis of OSA is made on the basis of nighttime and daytime symptoms, as well as abnormal polysomnographic findings. Asthma control, quality of life, and lung function were found to improve after initiation of CPAP therapy in asthma patients with moderate-to-severe OSA.[79]

Vocal cord dysfunction

Vocal cord dysfunction (VCD) is defined as abnormal adduction of the vocal cords resulting in airflow obstruction. The prevalence of VCD in patients with DCA is as high as 32%.[80] The most common symptoms are inspiratory dyspnea, wheezing and/or stridor in the neck, dysphonia, and hoarseness.[81] Common triggering factors include emotional stress, airway irritants, sudden changes in temperature, infections, and physical exercise.

Laryngoscopy is the gold standard for confirming a diagnosis of VCD[82,83] and must be performed during an attack, demonstrating abnormal adduction of the vocal cords during inspiration. Flattening of the inspiratory loop on the flow-volume curve on spirometry is suggestive of VCD.[84] Dynamic CT of the neck,[29] questionnaires,[85,86] and laryngoscopy during exercise can help to identify cases of VCD.[87]

There is no specific treatment for VCD. Treatment options include speech therapy (respiratory training and voice therapy), psychotherapy, and elimination of triggering factors.[72]

Other comorbidities

Dysfunctional breathing

The pathophysiology of dysfunctional breathing is poorly understood,[72] and dysfunctional breathing symptoms can be confused with asthma symptoms. Dysfunctional breathing coexists with DCA and is underdiagnosed.[88] On the basis of the Nijmegen Questionnaire,[89] the prevalence of dysfunctional

breathing in patients with DCA ranges from 30% to 64%.[80,90]

Dysfunctional breathing involves abnormal breathing patterns[91] described and classified elsewhere,[92,93] a disordered breathing pattern being a major component of dysfunctional breathing. The most well-known forms of dysfunctional breathing are hyperventilation syndrome and idiopathic hyperventilation.[94]

In asthma patients, dysfunctional breathing is associated with an increase in ER visits and unscheduled visits, as well as with activity limitations and impaired physical and mental health.[95,96] Dysfunctional breathing can coexist with other comorbidities, is common in patients with anxiety disorders such as panic disorder[97] and in those with VCD,[83,98] and is independently associated with worsening of quality of life and asthma control.[80]

Few studies have examined the treatment of dysfunctional breathing.[94] In patients with DCA, breathing exercises have been found to improve the Nijmegen Questionnaire score and asthma control, as well as reducing the frequency of exacerbations.[99]

Anxiety and depression

Patients with severe asthma are more likely to experience symptoms of anxiety and depression than are those with asthma that is less severe.[100] Although the prevalence of anxiety and depression symptoms in patients with severe asthma has been reported to be 38% and 25%, respectively,[101] anxiety and depression have been overlooked in the evaluation of DCA and severe asthma.[64] Anxiety and depression symptoms are associated with difficulty in controlling asthma,[102] increased use of health services,[103] near-fatal asthma attacks, and increased mortality.[104] These unfavorable outcomes might be related to poor adherence to the prescribed medication regimen, irregular medical follow-up care, and inappropriate asthma management practices.[105]

In a real-life study,[106] asthma control and quality of life questionnaires were found to correlate well with anxiety and depression scales. Therefore, patients with uncontrolled asthma and low quality of life should be screened for symptoms of anxiety and depression[106] and referred for follow-up in specialized centers.

GERD

GERD is a common comorbidity in patients with severe asthma.[68,107-109] A diagnosis of GERD is made on the basis of clinical symptoms, upper gastrointestinal endoscopy, and 24-h esophageal pH monitoring, with or without esophageal manometry and pH-impedance testing. Patients with DCA and symptoms of GERD should undergo treatment, which consists of lifestyle changes, pharmacological interventions, and, in some cases, surgery.[110]

Obesity

Evidence from cross-sectional studies suggests that obese individuals are at an increased risk for asthma.[111,112] Obese asthma patients have disease that is more severe, poorly controlled asthma, reduced quality of life, and increased ER visits and hospitalizations.[113-115] This might be due to several factors, including the type of inflammation, obesity-related comorbidities (OSA and GERD), and factors related to respiratory mechanics.

There is evidence that obesity increases the production of proinflammatory mediators in asthma, which are associated with visceral fat and can lead to increased BHR and bronchospasm.[116,117] Cross-sectional studies have suggested that obese asthma patients have predominantly neutrophilic airway inflammation.[117,118] This inflammatory pattern is predominantly seen in obese women with asthma, constituting the "asthma-obesity" phenotype.[71]

Weight loss should be included in the treatment plan for obese patients with severe asthma.[119,120] Weight loss can improve asthma control and lung function (FVC), as well as reducing the need for medications, without affecting inflammatory markers or markers of bronchial responsiveness.[120,121] Obese asthma patients who were enrolled in a weight loss and physical activity program and who lost 5-10% of their body weight were found to have improved asthma control and quality of life.[122] Bariatric surgery also results in improved asthma control, quality of life, and lung function.[4,123-125]

Figure 1 shows a flow chart for the management of DCA in adults.

BIOMARKERS

Biomarkers can help to identify different phenotypes and endotypes, as well as predicting the response to severe asthma treatment.[126] The most widely used biomarkers of type 2 (T2)-high inflammation are IgE, eosinophils in induced sputum (EosIS), eosinophils in peripheral blood (EosPB), and fractional exhaled nitric oxide (FeNO).[127]

IgE

IgE plays an important role in the pathogenesis of allergic asthma. Exposure to exogenous allergens triggers an inflammatory cascade with interleukins (IL-4, IL-5, and IL-13), as well as activation of different cells. IL-4 and IL-13 stimulate B lymphocytes to produce IgE.[128]

The allergic asthma phenotype is confirmed by clinical history and an immediate hypersensitivity response (a positive skin prick test), a positive specific serum IgE response to at least one aeroallergen, or a combination of the two. Age can affect IgE levels, and nonatopic patients can present with elevated IgE levels.[129] Diagnosis of the allergic asthma phenotype does not depend on total serum IgE; serum IgE, although, total serum IgE is used in order to calculate the dose of anti-IgE for the treatment of patients with severe asthma.

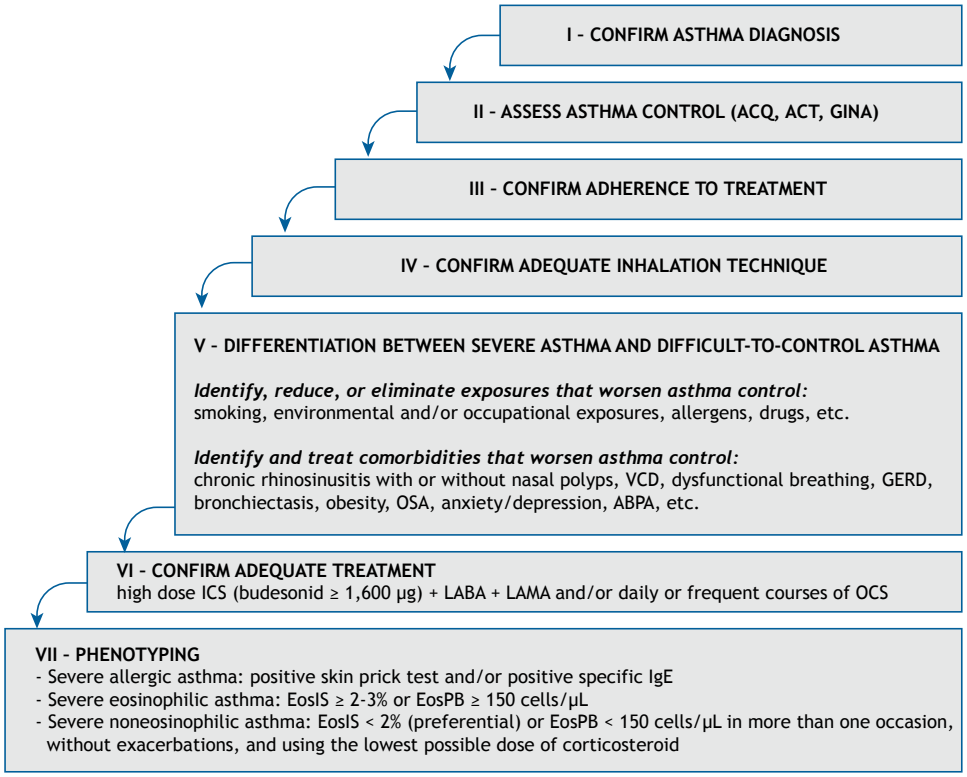

Figure 1. Flow chart of severe asthma diagnosis and phenotyping. ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; VCD: vocal cord dysfunction; GERD: gastroesophageal reflux disease; OSA: obstructive sleep apnea; ABPA: allergic bronchopulmonary aspergillosis; ICS: inhaled corticosteroid; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; EosIS: eosinophils in induced sputum; EosPB: eosinophils in peripheral blood; FeNO: fractional exhaled nitric oxide.

EosIS and EosPB

Induced sputum (IS) is a noninvasive method that allows quantification of airway inflammatory cells[130,131] and, consequently, identification of different phenotypes, although the cutoff point to characterize T2-high eosinophilic inflammation in asthma varies across studies (≥ 2% or ≥ 3%).[4,132]

In a study analyzing a database from the Belgian Severe Asthma Registry,[132] 55% and 21% of the patients, respectively, were found to have eosinophilic and nonesosinophilic asthma. In Brazil, the prevalence of inflammatory phenotypes in patients with severe asthma varies across cohorts, the eosinophilic phenotype having predominated in one study[70] and the noneosinophilic phenotype having predominated in another one.[133]

An increased percentage of EosIS (≥ 2% or ≥ 3%) is a predictor of response to ICS and OCS,[134] as well as of uncontrolled asthma and an increased risk of exacerbations.[135] The use of a therapeutic approach to maintain the percentage of EosIS below 3% has been reported to reduce the risk of exacerbations in comparison with standard management.[136-138]

Difficulties in implementing IS in clinical practice have led to a search for surrogate markers,[131] EosPB therefore being proposed as a simpler, cheaper, and more widely available option. Although EosPB counts partially correlate with EosIS counts,[139] eosinophilia in blood is also associated with increased severity and an increased risk of asthma exacerbation.[140] There is also evidence that an elevated EosPB count is associated with a better response to ICS.[141]

Caution is needed when interpreting EosPB counts because eosinophilia in blood can be caused by different diseases,[142] can vary over time,[143] and can decrease with the use of a corticosteroid, especially OCS.[144] In Brazil, a controlled study of individuals without asthma showed that major factors associated with increased EosPB were atopy, allergic rhinitis, and smoking.[145] Therefore, EosPB counts must be interpreted in the context of medical conditions and factors that can potentially influence EosPB levels.

For patients with severe asthma, the GINA suggests an EosPB count of ≥ 150 cells/µL as a cutoff point for detection of T2-high inflammation. Given the variability of EosPB counts, they should be performed at least three times and with the lowest possible dose of OCS.[4]

FeNO

FeNO is a noninvasive measurement of airway inflammation. An elevated FeNO is a marker of eosinophilic inflammation.[14] Although elevated FeNO and EosPB commonly occur concomitantly, these

biomarkers represent different aspects of T2-high inflammation.[146] An elevated FeNO correlates with increased lung function impairment[147] and more severe exacerbations.[148,149]

FeNO cutoff points vary across studies. Some guidelines state that, in adults, FeNO < 25 ppb is normal, FeNO > 50 ppb is high, and FeNO values of 25-50 ppb should be interpreted in association with clinical factors at the time of evaluation.[147,150,151] However, according to the GINA, FeNO ≥ 20 ppb characterizes T2-high inflammation.[14]

In addition to the wide variability of FeNO cutoff points, FeNO can increase or decrease as a result of factors such as use of ICS, OCS, or a combination of the two, as well as nonadherence to treatment.[152]

PHENOTYPING

Severe asthma is a complex heterogeneous disease with several different pathophysiological mechanisms and phenotypes, the identification of which can lead to successful targeted therapy.[1] A phenotype is defined as the observable characteristics of an organism that result from the interaction of its genotype with the environment.

Phenotyping based on the cellularity of the inflammatory response has resulted in the recognition of two major asthma phenotypes, namely, eosinophilic asthma and noneosinophilic asthma. Noneosinophilic asthma is associated with neutrophilic or paucigranulocytic inflammation.[153] Eosinophilic asthma is the more common phenotype, being found in most (70%) of the patients without previous treatment for asthma (i.e., treatment-naïve patients)[153-155] and in half of those undergoing treatment with corticosteroids.[132,156]

Severe asthma can also be classified by molecular phenotype (endotype), which is related to identification of a specific pathophysiological pathway for a given phenotype. The characteristics of a clinically useful endotype are as follows: a plausible molecular mechanism; longitudinal stability; correlation with relevant clinical outcomes; association with a biomarker that characterizes this pathophysiological pathway and that can be measured in practice; and response to targeted therapy.[1]

T2-high asthma is the best characterized endotype, resulting from the interaction between innate and adaptive immunity.[157] The T2-high endotype was initially designated Th2-high in recognition of the central role that Th2 lymphocytes play in the adaptive inflammatory response, with production of IL-4, IL-5, and IL-13 (Figure 2). However, the Th2-high asthma endotype was later designated T2-high asthma after evidence that innate immunity also plays an important role in this inflammatory pathway, with group 2 innate lymphoid cells (ILC2) producing large quantities of IL-5 and IL-13.[158,159]

The T2-high inflammatory response is mediated by Th2 lymphocytes and ILC2, as well as by IgE-producing B lymphocytes, eosinophils, mast cells, and basophils.[128,158] Whether the innate or adaptive immune response will predominate in the inflammatory response of asthma depends on the phenotype (i.e., allergic or nonallergic asthma).[160]

IL-4 is essential for the maturation of naïve lymphocytes into Th2 lymphocytes and for the switch of B lymphocytes to IgE-producing B lymphocytes. IgE binds to high-affinity receptors on basophils and mast cells, promoting their degranulation and thus releasing several proinflammatory mediators.[161] IL-5 is responsible for the recruitment, maturation, activation, and survival of eosinophils, which secrete several proinflammatory cytokines and chemokines.[128] IL-13 promotes fibrosis and smooth muscle remodeling and, together with IL-4, regulates IgE production and induces goblet cell hyperplasia, with increased mucus production. Mast cells produce prostaglandin D2, which binds to its receptor on Th2 lymphocytes, leading to the release of IL-5 and IL-9, which increase mucus production.[128,160,162] IL-4 and IL-13 also induce the expression of adhesion molecules in vascular endothelial cells, thus promoting the transmigration of eosinophils from the bloodstream to the airway tissue, which results in accumulation of eosinophils in the bronchial mucosa.[163]

Damage to the airway epithelium—the interface between the external and internal environments—leads to increased expression and release of IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), all of which stimulate ILC2 to produce IL-4 and IL-13 (Figure 2). Epithelial cell-derived cytokines, also known as alarmins, play an important mediating role in the inflammatory response to a variety of external stimuli, including allergens, viruses, bacteria, smoke, and pollutants.[128,158,160,164,165] At the same time, inadequate epithelial repair occurs, resulting in airway remodeling. In turn, airway remodeling leads to an increase in proinflammatory mediators, resulting in more inflammation and epithelial damage (Figure 2).[157]

The T2-high endotype is characterized by increased expression of IL-4, IL-5, and IL-13; airway and blood eosinophilia; airway epithelial dysfunction; and IgE production in the allergic phenotype.[1,158] This results in BHR, airflow obstruction, and exacerbations. The T2-high endotype is characterized by elevated biomarkers such as EosIS, EosPB, and FeNO.[157] It accounts for 50-75% of severe asthma cases.[166,167]

Although the T2-low endotype has yet to be completely defined, it is characterized by the absence of a T2-high inflammatory response. The pathophysiology of T2-low asthma has yet to be fully understood and is possibly associated with the activation of innate and acquired immune responses. The T2-low endotype includes neutrophilic asthma

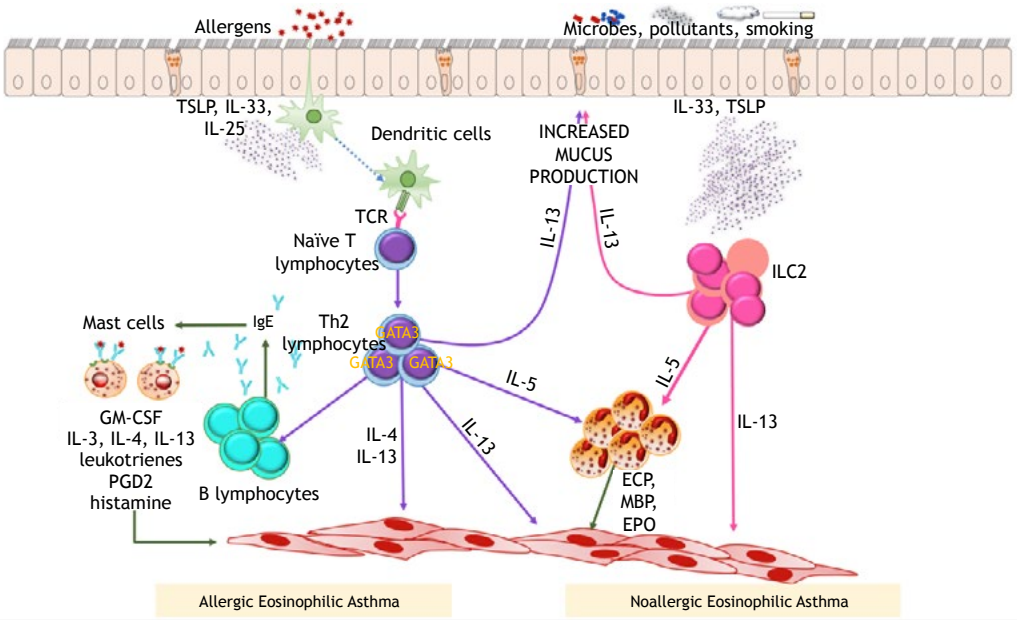

Figure 2. Inflammatory mechanisms of T2-high asthma phenotype. The figure schematically represents the main cells and cytokines involved in the adaptive and innate inflammatory response of the T2-high phenotype in severe asthma. In genetically susceptible individuals, inhalation of allergens (adaptive immunity), smoke, bacteria, and viruses (innate immunity) initiates and perpetuates the T2-high inflammatory cascade. TSLP: thymic stromal lymphopoietin; TCR: T-cell receptor; MHC2: major histocompatibility complex class 2; GATA3: transcription factor encoded by the *GATA3* gene; ILC2: group 2 innate lymphoid cells; PGD2: prostaglandin D2; ECP: eosinophil cationic protein; MBP: major basic protein; EPO: eosinophil peroxidase.

and paucigranulocytic asthma.[168] In patients with T2-low asthma, the gene-external trigger interaction can result in the production of alarmins (IL-33 and TSLP), which stimulate Th17 lymphocytes to produce IL-6, IL-8, and IL-17, all of which playing an important role in the attraction and stimulation of neutrophils. In addition, activation of Th1 lymphocytes can occur, stimulating neutrophilic inflammation via the production of TNF-α and INF-γ.[153]

Severe allergic eosinophilic asthma

Patients with allergic eosinophilic asthma have atopy, variable airflow obstruction, and bronchodilator response. They also have good response to ICS and present with eosinophilic inflammation associated with elevated total serum IgE levels and/or FeNO (≥ 20 ppb).[1,153] Patients with severe allergic eosinophilic asthma present with frequent exacerbations and do not always respond well to high-dose ICS alone or in combination with OCS, incomplete airflow reversibility occurring in some cases.

A confirmed diagnosis of severe allergic eosinophilic asthma requires an objective measure of atopy (skin prick testing and/or allergen-specific IgE in peripheral blood) and an increase in EosIS (≥ 2-3%) and/or EosPB (≥ 150 cells/μL).[4]

From a pathophysiological standpoint, airway inflammation in T2-high allergic asthma begins with repeated exposure of epithelial cells to inhaled allergens; in genetically susceptible individuals, this triggers an inflammatory response that is predominantly mediated by Th2 lymphocytes, IgE-producing B lymphocytes, eosinophils, mast cells, and basophils.[128] In this inflammatory pathway, dendritic cells present inhaled antigens to naïve T lymphocytes, which, in turn, switch to Th2 lymphocytes and starts producing IgE IL-4, IL-5, and IL-13. IL-4 stimulates the switch of B lymphocytes (Figure 2), which begin to produce IgE. IgE binds to high-affinity receptors on mast cells and basophils, which release inflammatory mediators (leukotrienes, prostaglandin, and histamine).[169]

Severe nonallergic eosinophilic asthma

Patients with nonallergic eosinophilic asthma usually have late-onset asthma associated with eosinophilic inflammation but not with atopy. This phenotype predominates in females and in asthma patients with chronic rhinosinusitis, with or without nasal polyposis, and/or obesity. In addition, these patients tend to have more severe airflow limitation, frequent exacerbations, and poorer response to corticosteroids.[1,153,158] The severe nonallergic eosinophilic asthma phenotype is confirmed by an increase in the percentage of EosIS (≥ 2-3%) and/or EosPB (≥ 150 cells/μL) in the absence of parameters for atopy.

In severe nonallergic eosinophilic asthma, ILC2 plays an important role (Figure 2). Nonallergic triggers, such as environmental or occupational pollutants, irritants, or microbes, stimulate airway epithelial cells to produce alarmins (TSLP, IL-33, and IL-25) which,

by activating ILC2, stimulate the production of IL-5 and IL-13 that induce eosinophilic inflammation.[153,169]

Severe noneosinophilic asthma

The T2-low endotype includes a heterogeneous group of asthma patients. In general, these patients present with highly symptomatic, late-onset disease, no atopy, and poor response to corticosteroids. This endotype is often associated with obesity.

The prevalence of severe noneosinophilic asthma phenotypes (neutrophilic or paucigranulocytic) varies between 30% and 50%.[167,170] The absence of T2 inflammatory characteristics may be due to several factors unrelated to the asthma endotype. Therefore, it is recommended that the diagnosis of severe noneosinophilic asthma be made only after excluding situations that may interfere with eosinophilia, such as the effect of corticosteroid treatment,[137,138,171] recent infections,[172,173] and exposure to occupational irritants or pollutants.[174,175]

Neutrophilic asthma

Neutrophilic asthma, whose pathophysiology is poorly understood, also involves innate and adaptive immunities. The diagnosis of neutrophilic asthma is confirmed by IS cell count confirming the absence of eosinophilia and the presence of neutrophilia (≥ 40-70%) more than once.[153,176] Neutrophilic IS is commonly associated with frequent respiratory infections, smoking, exposure to environmental or occupational pollutants, and, in some cases, chronic treatment with corticosteroids.[153] In individuals with neutrophilic asthma, the gene-external trigger interaction results in the production of alarmins (IL-33 and TSLP), stimulating Th17 lymphocytes to produce IL-6, IL-8, and IL-17, which play an important role in neutrophil attraction and stimulation. In addition, Th1 lymphocyte activation may occur, which also promotes neutrophilic inflammation via TNF-α and INF-γ production.[153]

The differential diagnosis of neutrophilic asthma includes persistent bacterial airway infections, nontuberculous mycobacteriosis, cystic fibrosis, primary ciliary dyskinesia, bronchiectasis, primary immunodeficiency, smoking, and COPD.[168]

Paucigranulocytic asthma

Paucigranulocytic asthma is uncommon. Diagnosis is made by the absence of eosinophilia and neutrophilia in IS. This pattern does not exclude airway inflammation, since this phenotype is accompanied by smooth muscle hypertrophy, remodeling, goblet cell hyperplasia, and BHR.[153]

PHARMACOLOGICAL TREATMENT OF SEVERE ASTHMA IN ADULTS

In recent years, important changes have taken place in the management of severe asthma in parallel with a better understanding of the pathophysiology and phenotyping of the disease. Current recommendations[2,14,151] for the treatment of severe asthma include high doses of ICS+LABA as the preferred treatment. In patients with uncontrolled asthma, LAMA and/or biologicals can be associated.

LAMA

LAMAs are long-acting bronchodilators that inhibit muscarinic acetylcholine receptors located in the airways. Consequently, they cause relaxation, decreased bronchial muscle tone, and decreased mucus secretion.[177] Several LAMAs (tiotropium, aclidinium, glycopyrronium, and umeclidinium bromides) are available or under study for the treatment of asthma.

Tiotropium bromide

At present, tiotropium bromide is the only LAMA approved for use in Brazil for the treatment of asthma. Evidence for tiotropium prescription as an additional treatment for uncontrolled, moderate-to-severe asthma (steps IV and V) are based on randomized controlled trials (RCTs) in adults and adolescents,[178-180] as well as in children.[181] In adults with severe uncontrolled asthma, the addition of tiotropium significantly increased lung function and decreased exacerbations.[182] This effect was similarly reported in two other studies in adolescents[178] and children[179] with severe asthma. In adults, these results were independent of baseline characteristics,[183] eosinophil counts, and serum IgE levels.[184]

Tiotropium is approved for the treatment of asthma of patients older than 6 years of age at a dose of 5 μg/day. This medication is recommended as an additional medication for patients with uncontrolled asthma who are already receiving moderate or high doses of ICS+LABA (steps IV or V).[2,4] Tiotropium has been shown to be a safe drug when added to other medications in asthma treatment.[178]

Other LAMAs

Evidence from RCTs suggests that other combinations of ICS+LABA or ultra LABA (indacaterol and vilanterol)+LAMA (umeclidinium and glycopyrronium) may be treatment options for severe asthma.[185-187]

Biologicals

In Brazil, four biologicals are approved for use in the treatment of severe asthma (omalizumab, mepolizumab, benralizumab, and dupilumab). Given the heterogeneity and complexity of severe asthma and assuming that the selected agent should target a particular phenotype/endotype (Chart 1), this approach requires experience. In addition, treatment with biologicals depends on differences in the local health care system, reimbursement policies, and accessibility; therefore, specialists should be responsible for this management.

Omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody that acts as an inhibitor of free IgE binding to

its high-affinity receptor on the membrane of mast cells and basophils. By means of this mechanism of action, IgE cannot act on effector cells, blocking degranulation and the consequent release of inflammatory mediators. It also promotes downregulation[188] of these membrane receptors, making them less numerous. Omalizumab does not alter IgE production, but it blocks free circulating IgE, forming immune complexes that will be eliminated by the reticuloendothelial system.[189] It is indicated for the treatment of severe allergic asthma (step V).[2,14,151]

Efficacy and effectiveness

Pivotal studies on omalizumab were carried out when the understanding of severe asthma differed from the current one. The most important study that comes close to the concepts used today is that by Humbert et al.[190] In this scenario, adding omalizumab to the combination of high-dose ICS+LABA reduced exacerbations by 26% and improved quality of life. However, a real-life study[191] showed that the inclusion of omalizumab for the treatment of severe asthma caused a 50-60% reduction in the exacerbation rate and a 50% reduction in the OCS dose.

A systematic review[192] that included 25 RCTs involving patients with moderate-to-severe allergic asthma showed that omalizumab, when compared with placebo, reduced exacerbations and hospitalizations and allowed a small reduction in the ICS dose. Another review[193] that included 42 real-life studies in adults and children with asthma showed that the addition of omalizumab in the treatment improved asthma control, reduced ER visits and hospitalizations, as well as the dose of ICS (mean reduction of 32% in the ICS dose). On average, 83% of patients were able to reduce or eliminate the use of OCS.

Predictors of response

Response to treatment with omalizumab has no predictor or single outcome, although patients with high EosPB and FeNO levels tend to have a better response.[194] The GINA suggests that EosPB ≥ 260 cells/μL and/or FeNO ≥ 20 ppb can be used as predictors of good response.[14] This document, in line with those by the ATS/ERS,[3] the British Thoracic Society,[195] and The National Institute for Health and Care Excellence,[196] questions the use of these biomarkers to assess the response to omalizumab, because the abovementioned cutoff points were derived from a retrospective analysis[194] and are in disagreement with the results of a real-life study,[191] which found no differences in the effect of omalizumab in patients with severe eosinophilic or noneosinophilic asthma. Therefore, the use of these cutoff values could limit the use of omalizumab to a group of patients who would eventually benefit from this treatment.

Indication

Omalizumab is recommended for patients with severe allergic 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 (Chart 2). However, the baseline IgE level does not characterize atopy and does not predict the response to treatment.[197] In addition, after starting treatment, that level should not be used as an indicator of response.[198] It is recommended that the efficacy of omalizumab be evaluated based on clinical outcomes at least 16 weeks after treatment onset.[199]

Safety

The most common adverse effects are local reactions. Anaphylaxis can occur in up to 0.2% of patients within the first 2 h of its administration, both in the first and in subsequent applications.[200] For this reason, it is recommended that the patient be monitored in an environment equipped for the treatment of this complication. The possibility of cardiac and cerebrovascular events should also be monitored.[201]

Mepolizumab

Mepolizumab is a fully humanized IgG1/k monoclonal antibody with high affinity for the IL-5 ligand, which inhibits IL-5 from binding with its alpha receptor epitope, blocking its activity and, consequently, the eosinophilic inflammatory response.[202]

Efficacy and effectiveness

RCTs have demonstrated that adding mepolizumab to the treatment of patients with severe eosinophilic asthma and frequent exacerbations reduced EosPB and exacerbations.[203-206] In patients with severe asthma and OCS-dependent, the median OCS dose reduction, in comparison with placebo, was 50%.[206] These benefits persisted for up to 4.5 years.[207]

The effectiveness and safety of mepolizumab have also been proven in real-life studies.[207-209] A British study including 99 patients with EosPB ≥ 300 cells/μL has demonstrated a 54% reduction in exacerbations. The use of mepolizumab reduced OCS doses in corticosteroid-dependent asthma patients, and the

Chart 1. Endotypes, phenotypes, and biomarkers.

Endotype	Phenotype		Biomarker
T2-high	Eosinophilic	Allergic	Positive specific IgE and/or positive skin prick test
		Nonallergic	EosPB or EosIS + negative specific IgE and/or negative skin prick test
T2-low	Noneosinophilic	Neutrophilic	Neutrophilia in IS + absence of T2 biomarkers
		Paucigranulocytic	Absence of eosinophilia and neutrophilia in IS + absence of T2 biomarkers

EosPB: eosinophils in peripheral blood, EosIS: eosinophils in induced sputum.

use of OCS could be discontinued in 57% of patients. Approximately 73% of patients were classified as responders and 28% as super-responders. Patients with nasal polyposis, better asthma control—determined by the Asthma Control Questionnaire with six questions (ACQ-6)—low BMI, and using OCS have shown to have the best treatment response.[208]

In a study,[209] the inclusion of mepolizumab in the treatment of patients with severe eosinophilic asthma (N = 309) showed that 86% were responders (reduction in symptoms and in exacerbations, as well as improvement in quality of life and lung function). After 12 months of treatment, 24% of the patients were considered super-responders (ACQ-5 < 1.0, no exacerbations, and OCS free).

Predictors of response

The main predictors of response to mepolizumab are EosPB ≥ 150 cells/μL,[210,211] presence of exacerbations in the previous year,[203] adult-onset asthma,[209] and presence of nasal polyposis.[212]

Indication

Mepolizumab is recommended for patients with severe eosinophilic asthma (≥ 150 cells/μL) ≥ 6 years of age. In 6-to 11-year-old patients, the dose is 40 mg, and in those > 12 years of age or who weighs > 40 kg, the dose is 100 mg, subcutaneously, every 4 weeks (Chart 2). It is recommended that its efficacy be evaluated based on clinical outcomes at least 12 weeks after treatment onset.[14,151]

Safety

The major adverse events are bronchial infections, irritation at the site of application, and headache. Anaphylaxis is rare.[14,151,213]

Benralizumab

Benralizumab is a monoclonal antibody that binds to the alpha chain of the IL-5 receptor, which blocks the effect of IL-5 on eosinophils, causing their apoptosis through cell-mediated cytotoxicity.[214] Benralizumab also significantly reduces eosinophils in the airways, bone marrow, blood, and IS.[215]

Efficacy and effectiveness

The efficacy of benralizumab has been proven in several RCTs[216-219] and in two systematic reviews.[220,221] Although phase III studies included patients with moderate-to-severe asthma,[216,217] a reanalysis of these studies evaluating only patients with severe asthma (according to the ATS/ERS criteria)[3] showed that the inclusion of benralizumab in the treatment of patients with EosPB ≥ 300 cells/μL reduced exacerbations and increased FEV1.[222] In OCS-dependent patients with severe asthma, the median dose reduction was 50% when compared with placebo.[223]

Real-life studies have confirmed the effectiveness of benralizumab in the management of severe asthma.[224,225] A British study including 130 patients with severe asthma and EosPB ≥ 400 cells/μL has demonstrated a 72.8% reduction in exacerbations. In 51% of corticosteroid-dependent patients the use of OCS could be discontinued. Patients were classified as responders (86%) and super-responders (39%), these responses being associated with higher EosPB and less severe disease (better FEV1, better asthma control, better quality of life, and lower dose of OCS).[225]

Predictors of response

The best predictors of response to treatment with benralizumab are chronic use of OCS, nasal polyposis, pre-bronchodilator FEV1 < 65% of the predicted value, and late-onset asthma.[222]

Indication

Benralizumab is recommended for patients with severe eosinophilic asthma ≥ 18 years of age.[2,14,151] It is administered subcutaneously at a dose of 30 mg. The first three applications are made every 4 weeks and, from the fourth application on, every 8 weeks (Chart 2). The first assessment of the response to treatment should be made at least after 12 weeks.[14,151]

Safety

The most common adverse events are nasopharyngitis, bronchial infections, reactions at the site of application, and headache. Anaphylaxis is rare.[219,226]

Dupilumab

Dupilumab is a human monoclonal antibody of the IgG4 class that binds to the alpha subunit of the IL-4 receptor, blocking common signaling for IL-4 and IL-13,[227] which are important mediators in T2 inflammation.

Efficacy and effectiveness

Initial studies with dupilumab in patients with uncontrolled, moderate-to-severe asthma showed a reduction in exacerbations, improvement in lung function, and asthma control.[228,229] The efficacy of dupilumab has been proven in a phase III RCT[230] with a 52-week follow-up that included asthma patients ≥ 12 years of age and uncontrolled, moderate-to-severe disease. When compared with placebo, dupilumab reduced exacerbations by up to 48%, increased FEV1 (140 mL difference in comparison with placebo), and improved symptoms and quality of life. When patients were stratified by EosPB, those with a level of ≥ 300 cells/μL had a more significant reduction in exacerbations (67%) and a greater increase in FEV1 (difference in relation to placebo of 240 mL). Dupilumab also reduced inflammatory markers (FeNO, IgE, and periostin).

Another RCT[231] including corticosteroid-dependent patients with severe asthma has demonstrated that dupilumab was effective in reducing the OCS dose (−70% vs. −42% when compared with placebo). In addition, the treatment reduced severe exacerbations

Chart 2. Biologicals for T2-high severe asthma endotype.

Parameter	Omalizumab	Mepolizumab	Benralizumab	Dupilumab
Age, years	≥ 6	≥ 6	≥ 18	≥ 12
Route of administration/dose	s.c. dose-dependent relationship with total serum IgE and body weight	s.c. 40 mg (6-11 years) and 100 mg (≥ 12 years or > 40 kg)	s.c. 30 mg	s.c. initial dose of 400 or 600 mg followed by 200 or 300 mg
Frequency of administration	every 2 or 4 weeks	every 4 weeks	First 3 doses every 4 weeks, followed by doses every 8 weeks	every 2 weeks
Eosinophils, cells/μL[a]	N/A	≥ 150	≥ 300	EosPB ≥ 150 (and/or FeNO ≥ 25 ppb)
Serum IgE, IU/mL	30-1,500	N/A	N/A	N/A

EosPB: eosinophils in peripheral blood, FeNO: fractional exhaled nitric oxide. [a]Based on pivotal studies.

by 59%, increased FEV1 by 220 mL, improved asthma control, and reduced FeNO. In that study,[231] the favorable effects were independent of the baseline levels of EosPB and FeNO. The beneficial effects of dupilumab have also been confirmed in a real-life study.[232]

Predictors of response

The major predictors of response to treatment with dupilumab are high EosPB levels and FeNO ≥ 25 ppb.[4]

Indication

In Brazil, dupilumab is recommended for patients ≥ 12 years of age and uncontrolled, severe eosinophilic asthma (elevated EosPB and/or FeNO). It is also recommended for patients on continuous use of OCS, regardless of baseline levels of EosPB and FeNO. The recommended initial dose is 400 mg subcutaneously, followed by 200 mg every 2 weeks. In corticosteroid-dependent patients and/or with comorbidities (atopic dermatitis, nasal polyposis, or eosinophilic esophagitis), an initial dose of 600 mg is recommended, followed by doses of 300 mg every 2 weeks (Chart 2).

Safety

In clinical studies, dupilumab was well tolerated and safe, and some patients may have a transient increase in EosPB.[230-232] Given that patients with baseline levels of EosPB > 1,500 cells/μL were not included in phase III clinical trials, there are no safety data for the use of dupilumab in this population, and, therefore, its use in these patients is not recommended to date.[233]

Azithromycin

The intermittent (250-500 mg three times/week) and prolonged (12 months) use of azithromycin as an additional therapy in uncontrolled severe asthma has been considered an option by various guidelines.[4,151,234] Azithromycin reduces exacerbations in other chronic neutrophilic respiratory diseases, including bronchiectasis and COPD.[168] However, its place in the prevention of exacerbations in severe asthma is still limited by the lack of robust scientific evidence regarding potential side effects. The use of azithromycin is off-label in asthma.[2,3,14]

Azithromycin is a macrolide antibiotic with antibacterial, antiviral, and immunomodulatory properties, the latter of which include inhibition of cytokines and chemokines, decreased expression of adhesion molecules, and increased neutrophil apoptosis.[235] However, the exact mechanism by which azithromycin is effective in preventing asthma exacerbations remains unclear.[168]

Although initial studies were directed toward noneosinophilic asthma and presented controversial results, RCTs produced evidence of the benefit of including azithromycin in the treatment of uncontrolled asthma.[236,237] In the largest of these studies,[237] 420 adults with uncontrolled, moderate-to-severe asthma were included. Add-on therapy with azithromicin reduced exacerbations by 40% and improved quality of life, showing similar efficacy on eosinophilic and noneosinophilic phenotypes.

Side effects of prolonged use of azithromycin include diarrhea, QT interval prolongation, hearing loss, and increased *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and nontuberculous mycobacteria (NTM) antimicrobial resistance. Performing an electrocardiogram prior to treatment onset is recommended to rule out active NTM infection. Sputum culture for NTM screening should be performed every 6 months in cases of prolonged treatment.[238]

HOW TO ASSESS RESPONSE TO TREATMENT WITH BIOLOGICALS IN SEVERE ASTHMA

Pivotal and real-life studies have shown that most patients with severe asthma with a T2-high profile, when properly investigated, phenotyped, and considered eligible for use of biologicals, respond well to treatment.[204,209,218,225,231] Patients are likely to respond to treatment in different ways, and direct comparative studies between different biologicals are unavailable. Therefore, the selection of a specific biological should be individualized according to the

possible predictors of response and accessibility to the medication.

Severe asthma patients should be evaluated more frequently, especially if they are using biologicals.[2] It is important to identify the objectives of treatment clearly and establish the parameters that will be systematically evaluated at each visit.

Although studies on how to assess the response to biologicals are scarce, this topic is extremely relevant in clinical practice. In order to propose a systematic approach for evaluating the response to treatment with biologicals, the present document was based on RCTs[202-205,215-218,228-230,238-241] and real-life studies.[193,208,209,225,243-246] RCTs have evaluated the effect of biologicals on one or more of the following outcomes: decrease in exacerbations, OCS-sparing effect, improvement of asthma control, increase in FEV1, and improvement in quality of life.[203,206,216-219,229-231,239-242] Real-life studies with a 24-48 week follow-up using inclusion criteria similar to those of RCTs identified responders, super-responders, and nonresponders to treatment.[208,209,225]

Responders

Responders[208,209,225,247] are patients with improved asthma control (a 0.5 point decrease in ACQ) and/or a reduction in exacerbations ≥ 50% and/or in the dose of OCS ≥ 50%.

Super-responders

Super-responders[208,209,225] are considered to be the patients with well-controlled asthma (ACQ < 1.5), free of exacerbations, and with a reduction in the dose of OCS ≥ 80% in corticosteroid-dependent patients.

Nonresponders

Nonresponders[209,247] are patients who fail to meet at least two of the following criteria: improvement in asthma control (0.5 point decrease in ACQ), reduction in exacerbations ≥ 50%, or reduction in the dose of OCS ≥ 25% in corticosteroid-dependent patients.

Figure 3 presents a suggestion of assessment of response to management of biological treatment between 6 and 12 months.

A few patients previously considered responders may, over time, have a poorer response, identified by a ≥ 25% reduction in baseline FEV1, the need to increase the dose of maintenance corticosteroids, or an increase of ≥ 0.5 point in the ACQ-5.[247] Clinical worsening can result from poor compliance, incorrect inhalation technique, occupational/environmental exposures, and infections. In such cases, chest CT and bronchoscopy may be necessary to investigate alternative or concomitant diagnoses. The production of antibodies against the biological can also be the cause of loss of response to treatment.[225,247,248]

In the absence or loss of response, treatment must be interrupted and the patient reassessed for the possible introduction of another biological. In cases of intermediate response, treatment can be continued for 12 months. When the response is adequate, treatment should be continued; if the response is inadequate, the use of another biological should be considered.[249]

Duration of treatment is yet to be established. However, it is known that interruption of treatment in responders is followed by eosinophilia[250,251] and exacerbations.[250]

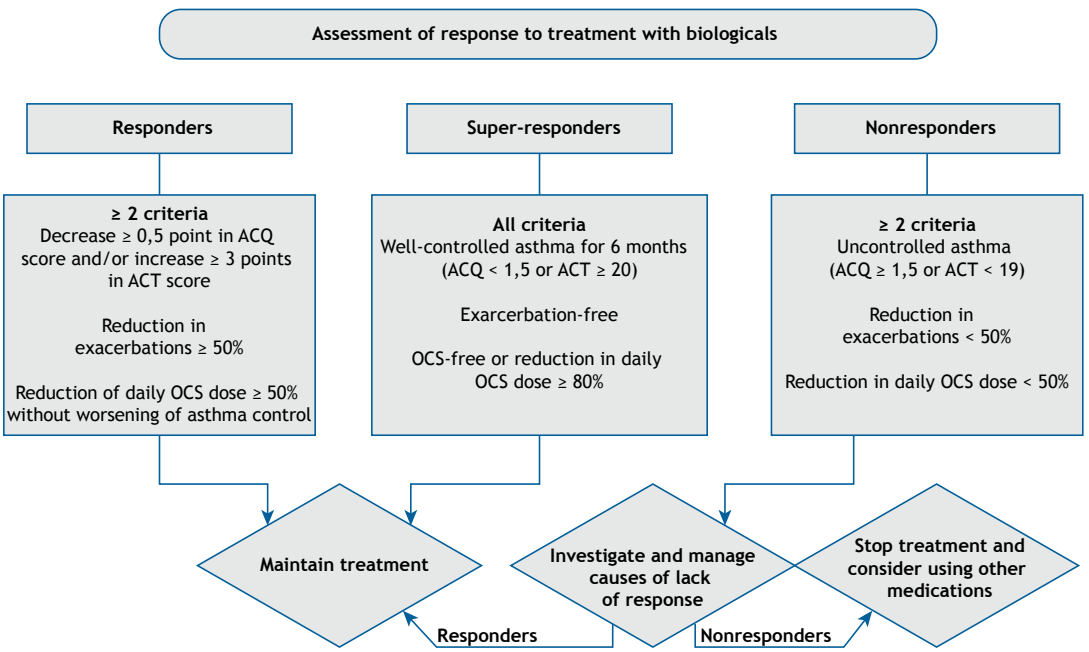

Figure 3. Assessment of response to treatment with biologicals. ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; OCS: oral corticosteroid.

Low-dose OCS

The use of OCS is an alternative option in step V with the lowest possible dose,[2,4] because the regular use or repeated courses of OCS is associated with serious adverse effects, although it is effective in achieving and maintaining asthma control.[252] Major adverse effects are bone mass loss and increased risk of bone fracture, body weight gain, metabolic syndrome, diabetes mellitus, systemic arterial hypertension, adrenal insufficiency, and immunosuppression.[3,9,14,151,253-255] These undesirable effects are dose-dependent.[256]

Gradual reduction and cessation of maintenance OCS

Due to the adverse effects of OCS, an attempt should be made to reduce its dose in all patients. No evidence-based guidelines on the best way to reduce OCS dose is available. However, expert recommendations[254] suggest that this should gradually be carried out up to a minimum effective dose or complete weaning of the medication has been reached. The pace and speed of dose reduction should be patient tailored, based on the history of severe exacerbations, prior treatment duration, and risk and type of adverse effects. Assessment of possible adrenal insufficiency during and after the OCS reduction process is recommended.[257]

NONPHARMACOLOGICAL TREATMENT

Bronchial thermoplasty

Bronchial thermoplasty is an approved nonpharmacological procedure for the treatment of uncontrolled, severe asthma patients being regularly treated.[258] By means of bronchoscopy, a catheter is inserted into the airways, generating radiofrequency energy and heating the bronchial walls in a controlled manner. The mechanism of action involves reduction of smooth muscle and airway nerve endings, as well as mechanical and physiological actions resulting from these reductions. The procedure must be performed in trained centers and consists of three sessions with intervals of 21 days.[259] Three RCTs[258,260,261] have investigated the safety and efficacy of bronchial thermoplasty, demonstrating improvement in quality of life and asthma control, as well as a decrease in exacerbations, emergency visits, hospitalizations, and OCS dose. These effects have been maintained for at least 10 years, with an acceptable safety profile.[262] Bronchial thermoplasty can be considered a treatment option for those patients with severe asthma who do not qualify for or adequately respond to treatment with biologicals.

Physical activity

The paradigm of exercise practice by patients with asthma began to change at the turn of the century with data from a systematic review[263] that compared studies that evaluated asthma patients participating in a physical training program with a group that did not perform physical activities. The group of asthma patients who performed exercises showed a significant improvement in aerobic capacity, but not in pulmonary function parameters assessed at rest.

In the following years, experimental studies have shown a reduction in IL-4 and IL-13 (pro-inflammatory cytokines) levels, suggesting an effect of physical training on reducing airway inflammation[264] and a significant increase in IL-10 (anti-inflammatory cytokine) expression.[265] The reduction in the levels of EosIS and FeNO were demonstrated in a clinical trial[266] that compared asthma patients who performed aerobic training with a control group, indicating that training reduced airway inflammation. However, this finding was not observed in a later study.[267]

A study that evaluated physical training programs for asthma patients has shown improvement in quality of life, as well as a decrease in anxiety/depression and asthma symptoms.[268] Another study showed that physical training improved asthma control and promoted weight loss and reduction of systemic and airway inflammation.[122]

A systematic review[269] including studies with adult asthma patients who underwent aerobic physical training demonstrated improvements in asthma control and pulmonary function. In obese asthma patients, physical exercise also helps with weight loss.[270]

Interventions aimed at promoting behavioral changes to improve physical activity in physically inactive adult patients with asthma have resulted in improvements in asthma control and a decrease in exacerbations, use of rescue medication and OCS bursts, as well as an increase in the practice of physical activities.[271] However, other studies have found no clinically significant improvements in asthma control with increased physical activity after interventions for behavioral change. This might indicate that clinical benefits are dependent on the magnitude of the increase in regular physical activity in asthma patients.[272,273]

Although supervised physical exercise based on structured programs might potentially improve asthma,[269] personal preferences of patients and barriers encountered in the practice of physical activity should be taken into account.[274] These findings point to the important role of physical activity in asthma management, indicating that the implementation of nonpharmacological measures, such as the practice of physical activity, needs to be considered together with pharmacological treatment in patients with severe asthma or DCA as well. The GINA recommends that adults with asthma engage in regular physical activity.[4]

DIAGNOSIS AND MANAGEMENT OF SEVERE ASTHMA IN CHILDREN AND ADOLESCENTS

Diagnostic aspects

The diagnostic criteria for asthma in children are the same as those established for adults. We emphasize, however, that in the 6- to 11-year age group, there are differences in lung function parameters: FEV1/FVC ratio < 0.9; reversibility to bronchodilator use > 12% of baseline values; mean variability of PEF > 13%; and > 12% reduction in FEV1 after exercise challenge

testing.[4] In addition, children with severe asthma do not commonly present with significant changes in or loss of pulmonary function.[275] Methacholine challenge testing should be restricted to cases with normal spirometry results and symptoms suggestive of asthma. A negative test result makes the diagnosis of asthma unlikely.[276]

The definition of severe asthma in patients between 6 and 11 years of age does not differ from that in adolescents and adults. However, it is important to highlight that ICS doses differ in this age group, being considered as a high dose > 400 µg/day of beclomethasone dipropionate (fine particle—hydrofluoroalkane) or equivalent.[4] Children suspected of having severe asthma should always be evaluated and managed by a specialist.[2,4]

The differential diagnosis of severe asthma in this age group includes cystic fibrosis, post-infectious bronchiolitis obliterans, foreign body aspiration, primary ciliary dyskinesia, congenital immunodeficiencies, congenital heart disease, among others.[4]

The investigation of severe asthma in this age group includes some aspects that are worth mentioning. There is no evidence to recommend routine chest CT. In severe asthma, CT should only be performed to exclude other diseases.[277] Investigation of gastroesophageal reflux should only be performed in selected cases. Treatment of asymptomatic gastroesophageal reflux rarely results in clinical improvement of asthma.[277] The risk of exacerbations is reduced by measuring FeNO levels to guide the pharmacological treatment in children.[278] Collection of IS is not recommended for pharmacological management in children.[279]

Severe asthma in children between 6 and 11 years of age should be phenotyped for a T2-high inflammatory profile using allergen sensitization testing, EosPB or EosIS (when available), and FeNO.[4] T2-high allergic eosinophilic asthma is the predominant phenotype in children with severe asthma.[280]

Treatment in children between 6 and 11 years of age

High doses of ICS+LABA are recommended for the treatment of severe asthma (step V) in children between 6 and 11 years of age. Prior to phenotyping, it is recommended to associate tiotropium with ICS+LABA in order to achieve and maintain asthma control.[2,281] Phenotyping is recommended in patients who do not achieve control.

In Brazil, two biologicals—omalizumab (anti-IgE) and mepolizumab (anti-IL-5)—have been approved for the treatment of asthma patients with the T2-high phenotype in this age group. The choice of the biological should be defined individually, considering biomarkers and access to treatment.

Efficacy and safety of omalizumab in children with severe asthma has been proven in an RCT[282] and in a real-life study.[283] A study in children and adolescents in Brazil showed that the inclusion of omalizumab in the treatment regimen improved asthma control and reduced hospitalizations and OCS dose.[284] Some children present with total IgE levels higher than the limits recommended in the manufacturer directions for omalizumab, contraindicating its use.[285]

Efficacy and safety of mepolizumab for children between 6 and 11 years of age was demonstrated in one study.[286] The doses of biologicals in this age group are described in Chart 2.

The response to treatment with biologicals should periodically be evaluated by means of objective measures of asthma control and reductions in exacerbations/hospitalizations and in the dose of OCS. Treatment duration in patients with good clinical response and recommendations on replacing biologicals in cases of treatment failure are yet to be established.

SUMMARY OF RECOMMENDATIONS FOR THE MANAGEMENT OF SEVERE ASTHMA

- Patients diagnosed with or suspected of having severe asthma should be referred to a specialist
- Adherence to treatment and proper inhalation technique must be verified at all medical visits
- Comorbidities and environmental/occupational exposures that may worsen asthma control should be investigated and, if present, eliminated or minimized
- Patients who need treatment with high-dose ICS (budesonide ≥ 1,600 µg or equivalent) associated with LABA and/or LAMA and/or antileukotrienes and/or OCS to maintain control or those whose asthma still remains uncontrolled should be considered as patients with severe asthma, due to the intrinsic severity of the disease
- The inclusion of tiotropium bromide in the treatment of severe asthma is recommended, preferably prior to the use of biologicals
- Patients with a confirmed diagnosis of severe asthma and a recommendation for treatment with biologicals should be phenotyped
- When available, IS analysis should be performed to phenotype severe asthma
- Measuring EosPB levels should be carried out for severe asthma phenotyping when EosIS analysis is unavailable
- Specific IgE and/or skin prick testing should be carried out for phenotyping all patients with severe asthma
- The total serum IgE level should be used to calculate the dose of omalizumab but not for phenotyping or treatment follow-up
- Routine use of FeNO for phenotyping or as a management strategy for severe asthma is not recommended
- The choice of the biological should be based on the phenotype and access to the medication
- The evaluation of response to treatment should be objective, using as parameters asthma control and reduction in exacerbations and of the dose of corticosteroids

- The treatment of responders should be continued indefinitely

AUTHOR CONTRIBUTIONS

RMCP, JEDC, MMMP, and JF: project conceptualization, methodology and administration; supervision; validation; and guarantors of the article. ASR, CAN, ÁAC, ALGF, AMSA, DCB, GCJ, LSBC, MFR, MBM, MAO, MAL, and PMP: drafting, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

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Predictive roles of D-dimer for mortality of patients with community-acquired pneumonia: a systematic review and meta-analysis

Cheng Yang[1], Han-Hua Zeng[1], Juan Huang[1], Qian-Yun Zhang[1], Kun Lin[2]

1. Department of Pulmonary and Critical Care Medicine, Meizhou People's Hospital, Meizhou, Guangdong, China.
2. Department of Preventive Medicine, Shantou University Medical College, Shantou, Guangdong, China.

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Study carried out in the Department of Pulmonary and Critical Care Medicine, Meizhou People's Hospital, Meizhou, China.

ABSTRACT

Objective: To explore the predictive roles of D-dimer for the mortality of patients with community-acquired pneumonia (CAP). **Methods:** This was a systematic review and meta-analysis. We searched the following databases: PubMed, EMBASE, Web of Science, Ovid MEDLINE, and Cochrane Library from their inception to July 26, 2020. Studies exploring the relationship between blood D-dimer levels and CAP-related mortality were selected. In this meta-analysis, we calculated mortality rates, sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios. **Results:** The search identified 1,073 articles, 8 of which (a total of 2,126 patients) were included in this meta-analysis. The pooled mortality rate of the overall sample was 0.10 (95% CI, 0.08-0.14). The levels of blood D-dimer in the nonsurvivors were significantly higher than those in the survivors (weighted mean difference = 1.03 mg/L [95% CI, 0.81-1.26]; $p < 0.00001$). The area under the summary ROC curve for the optimal cutoff value of D-dimer as a predictor of mortality was 0.848 (SE = 0.046), and the pooled negative likelihood ratio for D-dimer within the normal range was 0.24 (95% CI, 0.11-0.53). **Conclusions:** Blood D-dimer might be helpful for the initial assessment of mortality risk of patients with CAP. D-dimer levels within the normal range indicate low risk of mortality. Because of the small sample size in our study, our findings should be further explored and validated in future studies with larger sample sizes.

Keywords: Fibrin fibrinogen degradation products; Community-acquired infections/mortality; Pneumonia/mortality; Meta-analysis.

INTRODUCTION

As we all know, community-acquired pneumonia (CAP) has significant morbidity, mortality, and disease burden among adults ≥ 18 years of age.[1] Early assessment of CAP severity is very important for the management of CAP in adults.[2] The Pneumonia Severity Index (PSI) and the mental **C**onfusion, **U**rea, **Respiratory** rate, **B**lood pressure, and age ≥ **65** (CURB-65) score have been developed to predict CAP-related mortality in adults. Due to the lack of evidence of the effectiveness or safety of CURB-65, this score was conditionally recommended to determine whether hospitalization is required or not.[3] Although PSI is an effective and safe assessment tool, its rules are complicated and its application is time-consuming. Therefore, clinicians desire a simple test that could be helpful to predict CAP-related mortality. In addition, some studies suggested that proadrenomedullin, prohormone forms of atrial natriuretic peptide, cortisol, procalcitonin, copeptin, C-reactive protein, and IL-6 could also predict CAP-related mortality better.[4,5]

It is known that D-dimer is a specific product of fibrinolysis and can be tested quickly. Besides, D-dimer testing is commonly used. Some studies showed that the mean levels of D-dimer in nonsurvivors of CAP were significantly higher than were those in survivors of CAP and that D-dimer levels could be used to predict mortality in patients with CAP.[6-8] However, some investigators[9] suggested that the difference of mean D-dimer levels between CAP survivors and nonsurvivors was not statistically significant. So far, the effects of D-dimer levels on the prognosis of patients with CAP have yet to be systematically analyzed and discussed. Therefore, this systematic review and meta-analysis was conducted to explore the roles of D-dimer in predicting mortality in patients with CAP. It was hypothesized that elevated D-dimer levels might predict higher risk of mortality in patients with CAP.

METHODS

Protocol and registration

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Record ID: CRD42020188254) before this systematic review and meta-analysis was performed.

Search strategy

The search strategy was based on the following search items: ("Pneumonia" OR "Pneumonitis" OR

Correspondence to:
Qian-Yun Zhang. Department of Pulmonary and Critical Care Medicine, Meizhou People's Hospital, 63 Huangtang Rd, Meijiang District, Meizhou, 514031, China.
Tel.: 86 075 3220-2723. Fax: 86 075 3220-4840. E-mail: qianyunzhangmzh@163.com
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"Pneumonitides" OR "Pulmonary Inflammation" OR "Lung Inflammation") AND ("D-dimer Fibrin" OR "D-dimer Fragments" OR "Fibrin Fragment D1 Dimer" OR "Fibrin Fragment DD" OR "D-dimer" OR "Fibrin Fragment D-dimer" OR "Fibrin Fragment D"). Two of the authors searched the following databases: PubMed, Web of Science, EMBASE, Cochrane Library, and Ovid MEDLINE from their inception to July 26, 2020. In addition, manual retrieval of cross-references and related articles was performed as a supplement to the electronic search. When the same population was studied in twin studies, the most complete or the most recent one was included.

Inclusion and exclusion criteria

The inclusion criteria of studies were as follows: detecting blood D-dimer levels of adult patients with CAP; exploring the relationship between blood D-dimer levels and mortality of patients with CAP; and being published in English or Chinese.

The exclusion criteria of studies were as follows: overlapping or duplicate publications; article types such as abstracts, reviews, case reports, letters, or those based on animal experimental models; and studies involving children.

Data extraction

Data from the selected studies were extracted by the two of the researchers. If there were disagreements, they were resolved by a third researcher.

The extracted data included study characteristics (first author's name, year of publication, country, sample size, and mean age of the cohort), study design (retrospective or prospective), sample characteristics (sample collection time, type of specimen collected, and detection methods), mortality, and methods of D-dimer analysis (optimal cutoff threshold, normal range, and number of true positives, false positives, false negatives and true negatives, as well as mean D-dimer levels in survivors and nonsurvivors). We wrote to the authors of studies to ask for missing data when necessary. When no reply was received within four weeks, we used estimations based on the data available or the study was removed from the review.

Quality assessment

The same two researchers used the Newcastle-Ottawa Scale (NOS) to evaluate the methodological quality of the selected studies. Total scores of NOS range from 0 to 9; studies with scores ≥ 6 were considered high-quality studies.

Statistical analysis

D-dimer levels in survivors and nonsurvivors of CAP were quantitatively synthesized using the Review Manager program, version 5.0 (RevMan 5; Cochrane Collaboration, Oxford, UK). The weighted mean difference was used in order to compare continuous variables. Synthesized sensitivity, specificity, positive likelihood ratio (LR+), negative LR (LR−), diagnostic OR, and summary ROC (SROC) curve of cutoff and normal values for predicting CAP-related mortality (and their respective 95% CIs) were calculated using Meta-DiSc, version 1.4 (Cochrane Colloquium, Barcelona, Spain). When means and ranges were applied to continuous data, standard deviations were calculated in accordance with Hozo et al.[10] The chi-square test was used to assess statistical heterogeneity, which was quantified by *I2* between studies. Statistical significance was defined as $p < 0.1$ and *I2* >50%. The fixed-effects model was applied to the studies without significant heterogeneity, and the random-effects model was applied to the studies with significant heterogeneity. Sensitivity analysis was performed after eliminating the articles one by one (Review Manager) to estimate whether pooled results were stable or not. Potential publication bias was assessed by funnel plots.

RESULTS

Study selection

The search of the selected databases retrieved 1,073 studies, whereas no cross-references or related articles were selected for analysis. After removing 174 duplicates, the titles and abstracts of 899 articles were reviewed, and 822 were considered irrelevant to the research topic and were excluded. Of the 77 remaining articles that were carefully reviewed, 8 were included in the study. The flow chart of the study selection process is shown in Figure 1.

Characteristics of the included studies

The major characteristics of the studies[6-9,11-14] included in this review are shown in Table 1. Publication year of the studies ranged from 2003 to 2018. There were 7 prospective studies[6-9, 11,13,14] and 1 retrospective study.[12] Mean D-dimer levels of survivors and nonsurvivors of CAP were reported in 5 studies.[6-9,14] In order to predict CAP-related mortality, true- and false-positives and negatives were calculated in 3 studies[6,7,12] reporting optimal cutoff values (Table S1) and in 3 studies[11,13,14] reporting normal ranges (Table S2). The methods of D-dimer testing were reported in 7 studies,[6-9,11,13,14] but none of these studies reported whether blinded or independent measurements were performed or not. Follow-up was carried out from discharge to 90 days afterwards.

Methodological quality assessment of the studies

The NOS scores of the studies included in this review are summarized in Table 1. None of the studies provided information regarding confounding factors (baseline data, i.e., age) in patients with and without elevated D-dimer levels. Only 1 study explicitly described the method of assessing mortality.[13] Details on methodological quality assessment are shown in Table S3.

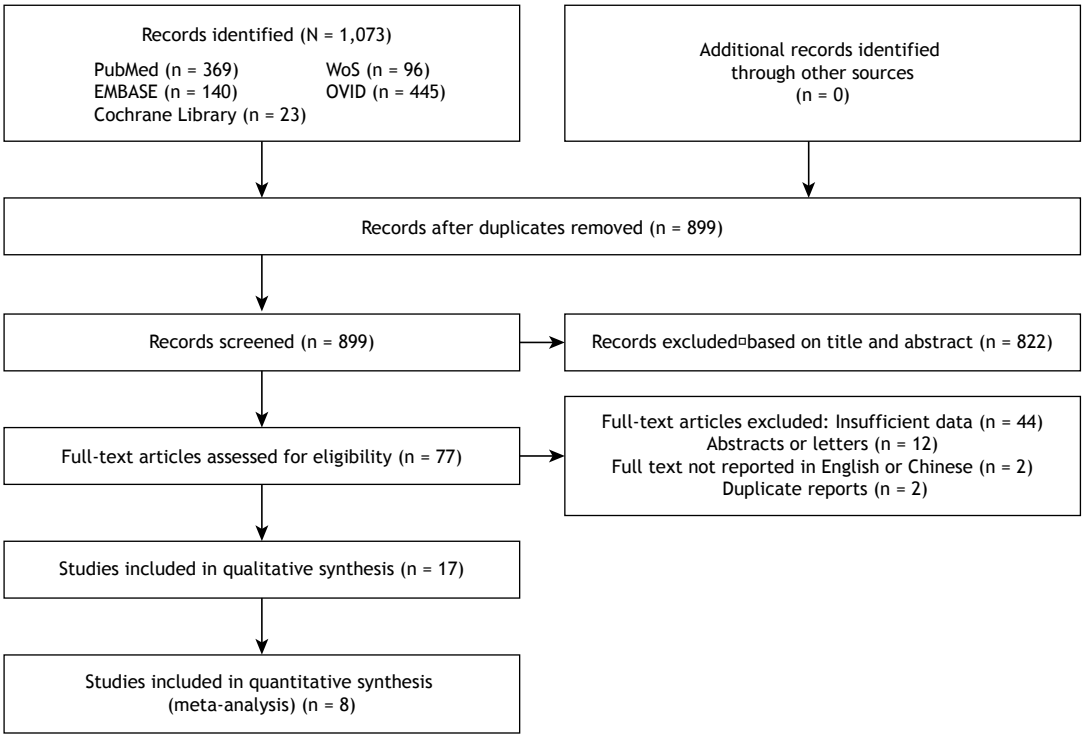

Figure 1. Flow chart of the study selection process. WoS: Web of Science.

Predictive value of D-dimer for CAP-related mortality

A total of 8 studies[6-9,11-14] involving 2,126 patients with CAP were included in this meta-analysis. The mortality of CAP patients ranged from 4.4% to 15.6%. The pooled mortality of the studies included was 0.10 (95% CI, 0.08-0.14; Figure S1). The pooled D-dimer levels in 507 patients from 5 studies[6-9,14] showed significant differences between survivors and nonsurvivors (weighted mean difference = 1.03 mg/L; 95% CI, 0.81-1.26; $p < 0.00001$; Figure 2). Three studies[6,7,12] reported optimal cutoff values of D-dimer for predicting CAP-related mortality: 2.0 mg/L[12]; 1.538 mg/L[7]; and 1.798 mg/L[6] (Table S1). Pooled results were as follows: sensitivity = 0.75 (95% CI, 0.63-0.85; Figure 3A); specificity = 0.82 (95% CI, 0.79-0.85; Figure 3B); LR+ = 3.88 (95% CI, 2.34-6.42; Figure 3C); LR− = 0.31 (95% CI, 0.20-0.47; Figure 3D); diagnostic OR = 12.65 (95% CI, 7.09-22.57; Figure 3E); and AUC = 0.848 (SE = 0.046; Figure 3F). Three studies[11,13,14] reported the normal range of D-dimer levels for predicting CAP-related mortality (Table S2). Pooled results were as follows: sensitivity = 0.96 (95% CI, 0.90-0.99; Figure 4A); specificity = 0.21 (95% CI, 0.19-0.24; Figure 4B); LR+ = 1.21 (95% CI, 1.10-1.33; Figure 4C); LR− = 0.24 (95% CI, 0.11-0.53; Figure 4D); and diagnostic OR = 4.97 (95% CI, 2.19-11.27; Figure 4E).

Sensitivity analysis and publication bias

A sensitivity analysis was conducted on the sequential exclusion of studies for each index, and none of these exclusions affected the results significantly, indicating that the results of the present study are relatively stable. The funnel plot of the 8 studies included in the analysis showed no obvious asymmetry (Figure 5), which suggests that publication bias was not significant.

DISCUSSION

Five studies[6-9,14] showed that, when compared with survivors of CAP, nonsurvivors had much higher blood D-dimer levels. The results showed that the optimal cutoff value of D-dimer had high pooled specificity and relatively low pooled sensitivity for predicting mortality. In contrast, normal D-dimer values in blood had very high sensitivity and very low specificity.

The CAP-related mortality of hospitalized patients was estimated to be between 6% and 20%,[15] which varied greatly depending on treatment setting, disease severity, and follow-up period. In our study, the pooled CAP-related mortality was 10% (95% CI, 0.08-0.14), which was basically consistent with the previous results.

D-dimer includes multiple specific peptide fragments produced by the degradation of cross-linked fibrin. It is commonly used for the diagnosis of pulmonary embolism. The procoagulant responses of the patient are closely associated with inflammatory reaction to infection.[16] A study[17] recruiting 684 ER patients with infection or sepsis, 19% of whom were diagnosed with CAP, revealed that high D-dimer levels were related to 28-day mortality. In addition, it has been reported that sepsis induced a coagulopathy score

Table 1. Characteristics of the studies included in the analysis.

Study	Year of publication	Country	Sample size	Age, years[a]	P/R	Clinical setting	Optimal cutoff value	Normal range	Blood collection	Type of specimen	Detection method	Hospital setting	Mortality rate, % (n/N)	Primary outcome	NOS score
Chalmers et al.[11]	2009	United Kingdom	314	61 [42-73]	P	CAP	N/A	0-0.5 mg/L	On admission	N/A	ELISA	Teaching hospital	7.0 (22/314)	30-day mortality	5
Dai et al.[12]	2018	China	230	82 [74-87]	R	CAP with COPD	2.0 μg/mL	N/A	N/A	N/A	N/A	A tertiary specialized teaching hospital and a secondary hospital	6.6 (19/290)	In-hospital mortality	6
			290	79 [67-86]		CAP without COPD							8.3 (19/230)		
Milbrandt et al.[13]	2009	USA	732	N/A	P	CAP	N/A	0-0.256 mg/L	ER admission	Plasma	Latex immunoassay	Academic and community hospitals	11.5 (84/732)	90-day mortality	7
Nastasijević Borovac et al.[7]	2014	Serbia	129	64.8 ± 13.3	P	CAP	1.538 mg/L	N/A	On admission	Plasma	Quantitative latex method	Teaching hospital	10.1 (13/129)	Mortality	4
Salluh et al.[6]	2011	Brazil	90	73.5 [57.7-83.0]	P	Severe CAP	1.798 mg/L	N/A	First day of ICU admission	N/A	Immunoturbidimetry	Tertiary hospital	15.6 (14/90)	In-hospital mortality	6
Shilon et al.[9]	2003	Israel	68	67.0 ± 20.8	P	CAP	N/A	0-0.375 mg/L	At admission	Plasma	Miniquant D-dimer assay	Primary care hospital	4.4 (3/68)	In-hospital mortality	7
Snijders et al.[14]	2012	The Netherlands	147	63.1 ± 17.8	P	CAP	N/A	0-0.5 mg/L	First day of admission	Serum	ELISA	A teaching hospital	5.4 (8/147)	30-day mortality	6
Xu et al.[8]	2017	China	126	62.5 ± 8.9	P	CAP	N/A	N/A	N/A	Serum	Immunoturbidimetry	A tertiary hospital	14.3 (18/126)	In-hospital mortality	6

P: prospective; R: retrospective; NOS: Newcastle-Ottawa Scale; and CAP: community acquired pneumonia. [a]aValues expressed as median [IQR] or mean ± SD, except where otherwise indicated.

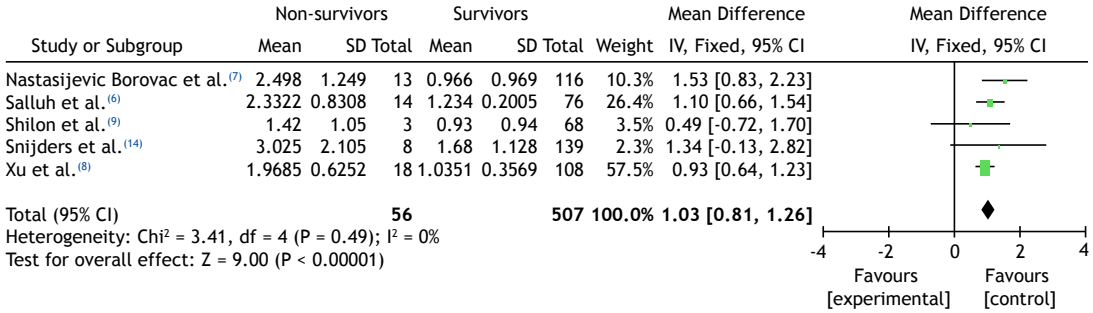

Figure 2. Meta-analysis and forest plot of D-dimer levels in the survivors and non-survivors.

> 4 and elevation of D-dimer levels (more than six times the reference value), which was associated with a worse prognosis of severe COVID-19.[18] What is more, another study suggested that an increase in D-dimer levels is the most significant change in coagulation parameters in patients with severe COVID-19, and progressively increasing values can be used as a prognostic parameter of a worse outcome.[19] D-dimer levels could be extremely useful to identify patients who could be potential targets for therapeutic interventions aimed at resolving coagulation disorders, such as heparin or recombinant activated protein C. Our pooled data showed that nonsurvivors of CAP had higher D-dimer levels than did survivors of CAP, which suggested that elevated D-dimer levels might be related to a higher risk of death in patients with CAP.

The most commonly used tools for the initial evaluation of CAP are CURB-65 and PSI. The use of PSI increased the proportion of low-risk patients who were safely treated on an outpatient basis.[3] Our meta-analysis found that D-dimer values within the normal range might help identify low-risk CAP patients. The prognostic models of PSI and CURB-65 were applied to immunocompetent patients with pneumonia from diagnosis in order to predict 30-day mortality.[3] A meta-analysis[20] found that the AUC of the SROC curve of PSI was 0.81 (SE = 0.008) for predicting CAP-related mortality and that the cumulative mortality rate was 8.3%. The present study pooled the optimal cutoff value of D-dimer and showed that the AUC was good (AUC = 0.848; SE = 0.046).

It was reported that the detection of D-dimer levels in CAP patients might affect diagnostic procedures for venous thromboembolism (VTE) and might even cause the use of unnecessary and expensive tests.[21] However, when VTE is excluded, D-dimer has much more significance in the comprehensive clinical evaluation.[22,23] Elevated levels of D-dimer might remind the clinician to assess the risk of VTE in those patients. Therefore, the addition of D-dimer testing to the diagnostic algorithm has the potential to make the diagnosis of deep vein thrombosis (DVT) in outpatients more convenient and economical. However, patients with D-dimer levels higher than reference levels are not systematically assessed to detect whether VTE is present or not. This means that undetected VTE might cause CAP-related mortality of patients.[21] On the other hand, since DVT cannot be diagnosed by clinical evaluation alone, when patients have D-dimer levels within the normal range, DVT can be excluded.[24] Therefore, "normal" D-dimer levels could be used to predict the prognosis of CAP, without being affected by DVT. In the present study, the pooled LR− of "normal" D-dimer level was 0.24 (95% CI, 0.11-0.53), which was similar to that of CURB-65 scores 0-1 (LR− = 0.21 [95% CI, 0.15-0.30]) in a previous study,[20] indicating that D-dimer levels within the normal range are useful to identify CAP patients with a low risk of mortality.

The heterogeneity between studies was significant regarding some variables. Different methods of D-dimer testing, blood sample collection, severity of CAP, and age distribution might bring about the obvious heterogeneity. Therefore, the random-effects model was applied to the pooled data, which could reduce the effect of heterogeneity, but not eliminate it.

Although our study cannot prove that D-dimer levels can be used as a single biomarker replacing the classical, well-validated scores, D-dimer can be quickly quantified, and using D-dimer levels together with PSI might help predict CAP-related mortality, improving the treatment and management of the disease more accurately and scientifically.

In the present study, there were several limitations. First, the major limitation was that the methodological quality of the studies included in the analysis was generally low, the comparability scores of all of which being equal to zero, and none provided information information about blinding methods. Second, there was high heterogeneity among the studies, and, thus, the results should be interpreted with caution. Third, pulmonary embolism or thromboembolism were not listed as an exclusion criterion in 5 of the studies.[6,9,12-14] Fourth, most of the studies were single center studies, which might have caused admission or selection bias. Last but not least, the small sample size and the small number of studies reduced the applicability of this meta-analysis. Nevertheless, multiple strategies were used for selecting studies, and strict criteria were adopted to evaluate their

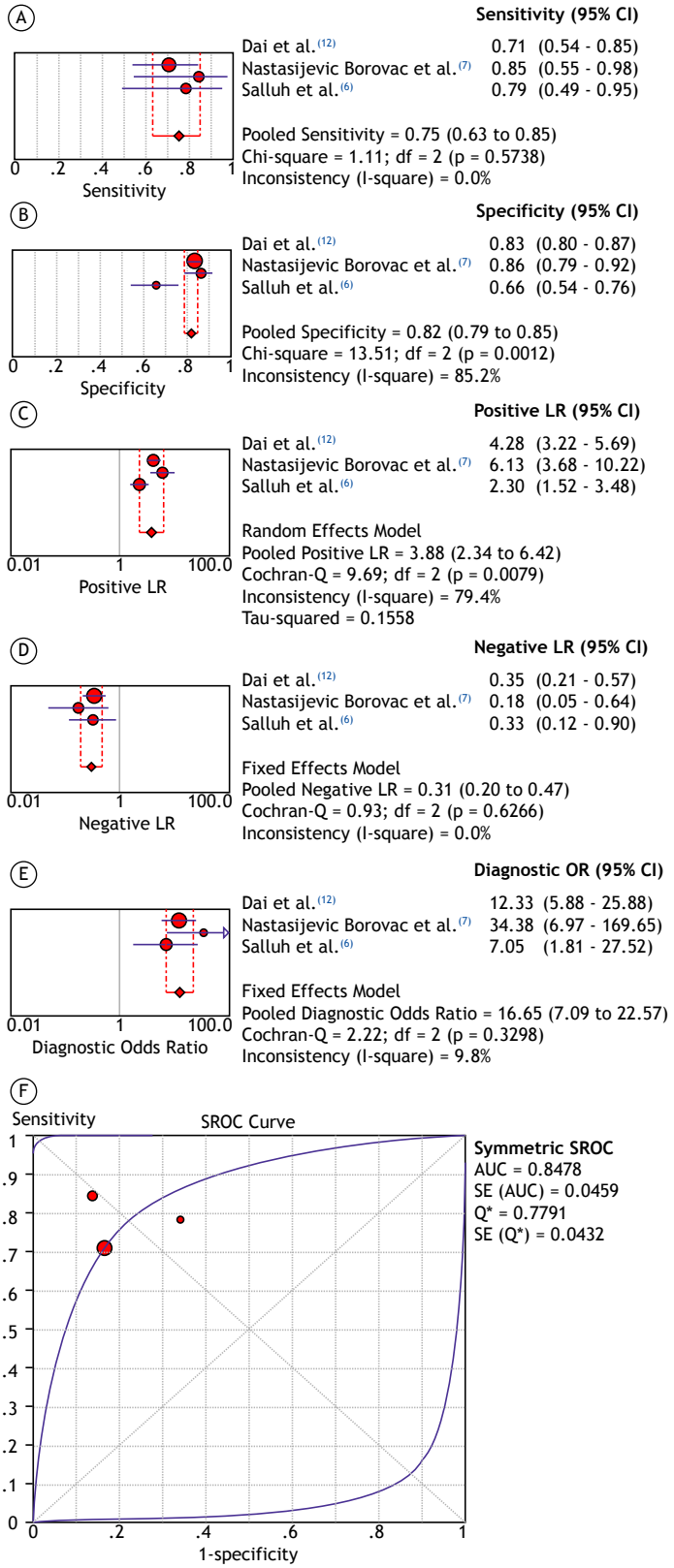

Figure 3. Optimal D-dimer cutoff values for predicting mortality. Forest plot and meta-analysis of sensitivity, in A; specificity, in B; positive likelihood ratio (LR) in C; negative LR, in D; diagnostic odds ratio, in E; and summary ROC curve, in F.

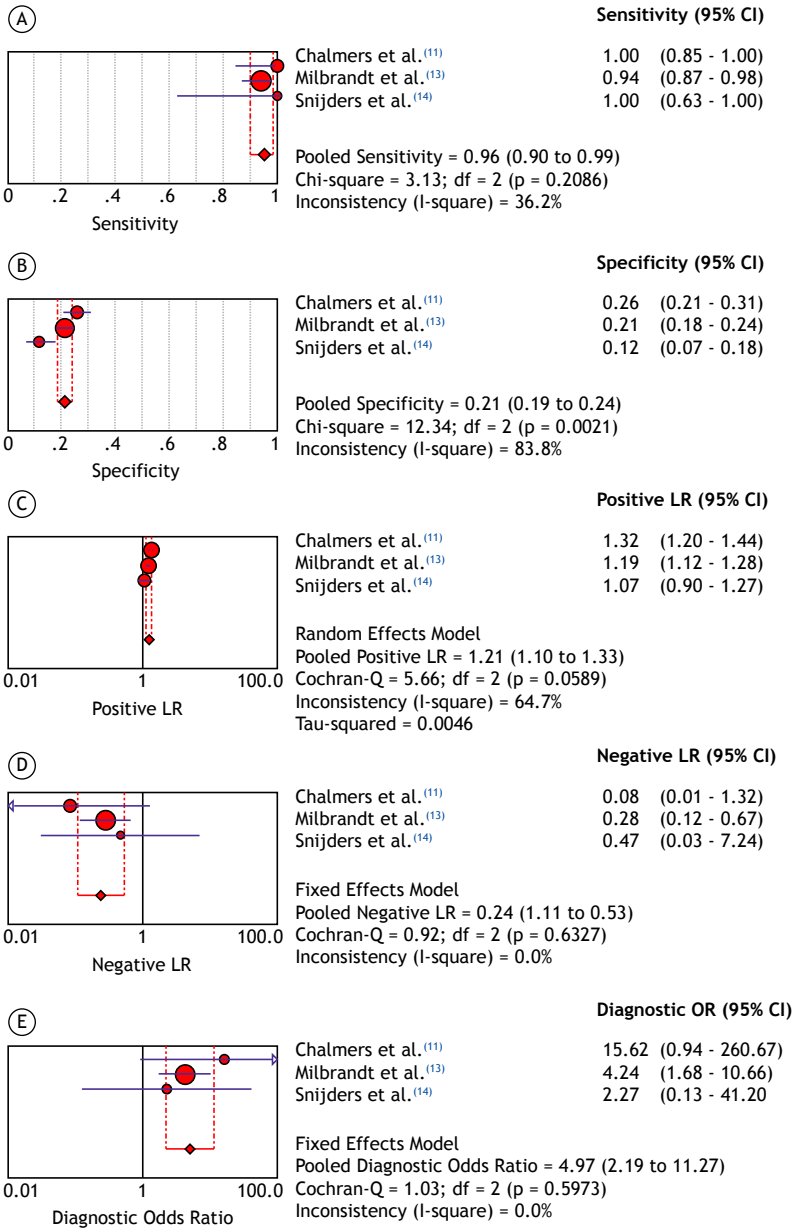

Figure 4. Normal D-dimer values for predicting mortality. Forest plot and meta-analysis of sensitivity, in A; specificity, in B; positive likelihood ratio (LR) in C; negative LR, in D; and diagnostic odds ratio, in E.

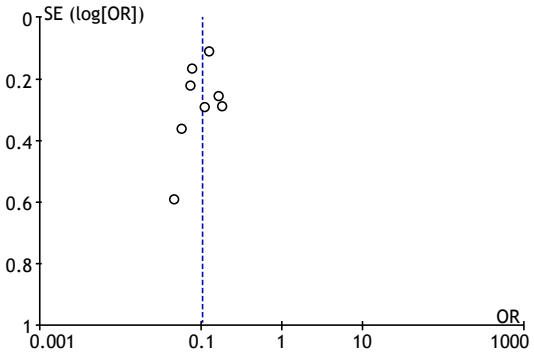

Figure 5. Funnel plot of publication bias.

methodological quality. The studies included in the analysis were carried out in seven countries from different continents, reducing publication bias. Thus, our results can be considered reliable.

In conclusion, as a biomarker, blood D-dimer may be helpful for the initial assessment of mortality risk of CAP patients, especially for identifying patients with a low risk of death when their D-dimer levels are within the normal range. However, well-designed prospective studies will be still necessary to explore the value of blood D-dimer levels for predicting CAP-related mortality in different clinical settings in the future.

AUTHOR CONTRIBUTIONS

CY: study conception and design; data collection; data analysis and interpretation; drafting and revision of the manuscript; and approval of the final version. HHZ, JH, and QYZ: data collection; data analysis and interpretation; and approval of the final version. KL: study conception and design; critical review for intellectual content; and approval of the final version.

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Malignant pleural mesothelioma: an update

Glaucia N. M. Hajj[1,2], Carolina H. Cavarson[1,2], Clóvis Antônio Lopes Pinto[3], Gabriela Venturi[1,4], João R. Navarro[4], Vladmir C. Cordeiro de Lima[2,5]

1. Instituto International de Pesquisa, A.C. Camargo Cancer Center, São Paulo (SP), Brasil.
2. Instituto Nacional de Oncogenômica e Inovação Terapêutica, São Paulo (SP), Brasil.
3. Departamento de Patologia Anatômica, A.C. Camargo Cancer Center, São Paulo (SP), Brasil.
4. BP Mirante, São Paulo (SP), Brasil.
5. Rede D'Or, São Paulo (SP), Brasil.

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ABSTRACT

Malignant mesotheliomas are rare types of cancers that affect the mesothelial surfaces, usually the pleura and peritoneum. They are associated with asbestos exposure, but due to a latency period of more than 30 years and difficult diagnosis, most cases are not detected until they reach advanced stages. Treatment options for this tumor type are very limited and survival ranges from 12 to 36 months. This review discusses the molecular physiopathology, current diagnosis, and latest therapeutic options for this disease.

Keywords: Pleural Mesothelioma; Treatment; Molecular Alterations.

INTRODUCTION

Malignant mesothelioma (MM) is a rare type of cancer associated with occupational or environmental asbestos exposure in 80% of cases.[1] The first case of MM associated with asbestos was reported in the USA, in 1967, due to an epidemic event of MM among miners, which helped to establish the association between asbestos exposure and the disease development. Hitherto rare, MM incidence has been increasing since the second half of the 20th century, a context in which MM has been linked to the indiscriminate use of asbestos over the last century.[2] The true extent of such worldwide MM epidemic is unknown. Currently, the greatest burden of asbestos use concentrates in Brazil, Russia, India, and China.[3]

The pleura is the most common site of MM origin (73-85%), followed by the peritoneum (7-18%).[4-6] MM predominantly affects males (male to female ratio 5:1), and the risk increases with age, with a higher prevalence in individuals >65 years of age.[7,8]

United Kingdom, Australia and New Zealand have the highest MM incidence rates, while Japan and Central European countries hold the lowest values.[9] It is estimated that between 2005 and 2050, approximately 94,000 cases of MPM and 15,000 cases of malignant peritoneal mesothelioma will have been diagnosed in the USA.[10]

Brazil is considered one of the most important producers and exporters of asbestos. MM mortality rate has steadily increased in Brazil, from 0.64 deaths per million population in 1980 to 1.18 deaths per million population in 2002. From 1980 to 2010, a total of 3,718 deaths from mesothelioma were recorded, mostly (2,180) occurring in the southeast of the country. The mortality rate between males and females was balanced, and 80.7% of deaths occurred in people older than 50 years. Nevertheless, a large number of patients remain undiagnosed, resulting in the current low MM incidence in Brazil.[11-13]

Germline mutations in cancer predisposition genes are reported in approximately 12% of MPM patients, being more common in younger patients, women, with little or no exposure to asbestos, and those with family history of cancer or individual history of cancer (melanoma, mesothelioma, breast cancer). *BAP1* is the most frequently mutated gene in this scenario, accounting for 3-7% of the cases.[14-16]

THE ROLE OF ASBESTOS IN MESOTHELIOMA PATHOGENESIS

Asbestos is the generic name of six varieties of fibrous minerals found in igneous and metamorphic rocks: Chrysotile (serpentine – white asbestos), Amosite and Actinolite (amphibole – brown asbestos), and Anthophyllite, Crocidolite, and Tremolite (blue asbestos).[14] The association between exposure to amphiboles and malignant pleural mesothelioma (MPM) is well described, and Crocidolite is considered the most oncogenic. It is believed that the thinner and longer (especially those longer than 8.0μm and wider than 0.25μm), the more dangerous the fibers, since they persist longer in the pleura, penetrate into the lungs, causing repeated tissue damage and repair, in addition to local inflammation.[17] Exposure to asbestos and other fibrous minerals can cause asbestosis, lung cancer, benign pleurisy, pleural plaques, and MPM.[18,19] In contrast, asbestos exposure is only very weakly associated with peritoneal malignant mesothelioma (33-50% of

Correspondence to: Glaucia Noeli Maroso Hajj. Centro Internacional de Pesquisa e Ensino, AC Camargo Cancer Center, R. Taguá, 440, Liberdade, CEP: 01509-010, São Paulo, SP, Brazil.
Tel.: 55 011 99113-1337. E-mail: ghajj@accamargo.org.br
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patients report previous asbestos exposure) and the timing and duration of exposure do not directly correlate with disease development.[9]

Although the association between asbestos exposure and mesothelioma pathogenesis is widely accepted, a common hypothesis has not been reached to explain it. Up to 80% of MPM patients have been previously exposed to asbestos. However, the reason for only a small proportion of asbestos-exposed individuals develop MM (2-10%) remains unknown.[17] (Figure 1).

Mesothelial cells (MC) are highly susceptible to asbestos cytotoxicity, and many pathogenic events may contribute to carcinogenesis during the long latency period between asbestos exposure and tumor development.[20] MC is affected by various cellular changes induced by asbestos, such as DNA damage, cell cycle inhibition, and apoptosis.[21-24] Conversely, MC produces many inflammatory mediators in response to asbestos.[25]

The mechanisms through which inflammation affects the development of MM are not fully understood, but growing evidence has supported a link between the local and systemic inflammatory response and patient prognosis.[26] The presence of an intense and sustained systemic inflammatory response characterized by leukocyte migration and cytokine secretion promotes

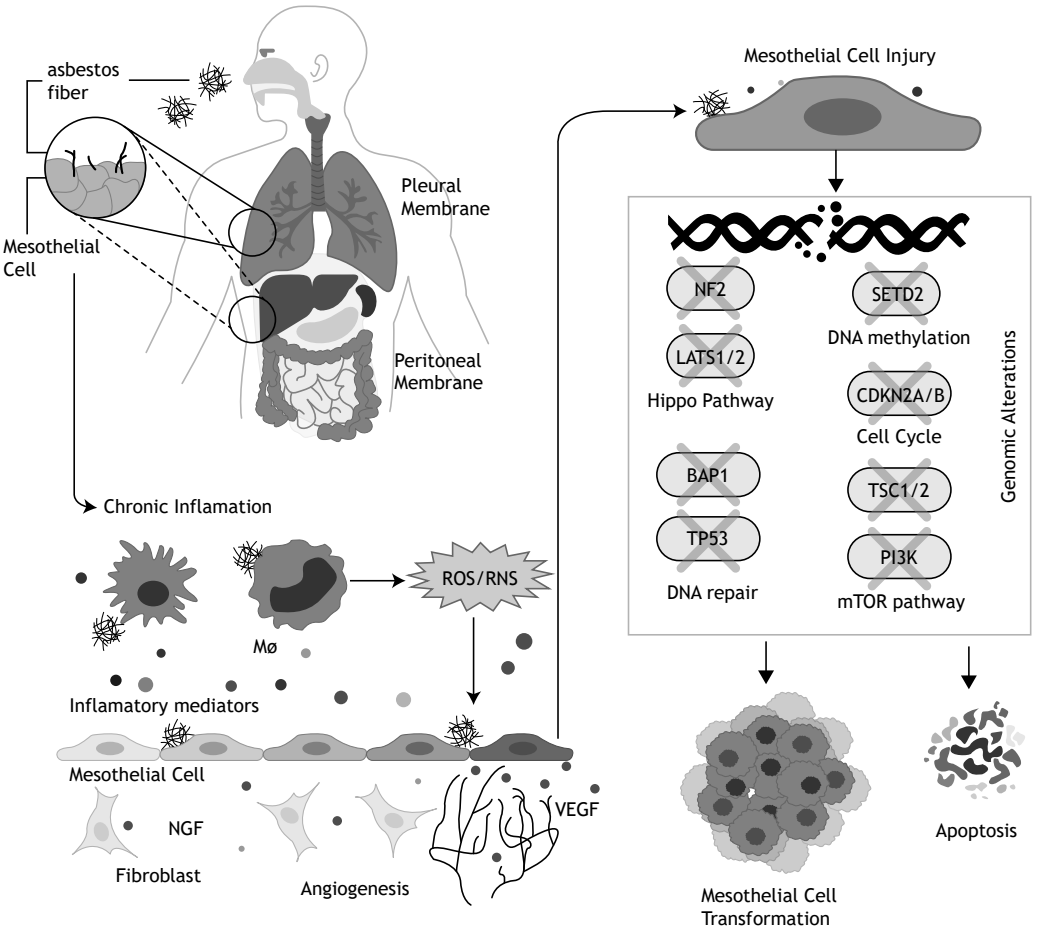

Figure 1. Molecular mechanisms associated with MM pathogenesis. Inhaled asbestos fibers transverse terminal airways and lodge themselves in the pleural space. Macrophages try to phagocytize these fibers without effect and in doing that they release reactive oxygen species and reactive nitrogen species, which may promote genotoxic damage, and recruit other inflammatory and immune cells. Repeated DNA damage by ROS and RNS may lead to the accumulation of oncogenic mutations in the mesothelial cells. The genes most frequently mutated in mesothelioma and that may be associated with malignant transformation of mesothelial cells are involved with DNA repair, the Hippo pathway, cell cycle control, DNA methylation and the mTOR pathway. Germ line mutations in genes associated with DNA repair (*BAP1, BRCA1, CHECK2*, etc) are found in 12% of mesothelioma patients and are associated with earlier disease onset and good prognosis. In parallel, the inflammatory mediators released in the microenvironment may promote cell survival (inhibiting apoptotic signals) and stimulate mesothelial cell proliferation (even in the presence of DNA damage), activate fibroblast to produce extracellular matrix proteins, and promote neoagiogenesis. These modifications favor tumor growth and create an immunossupressive milieu. Mø-macrophages; ROS-reactive oxygen species; RNS-reactive nitrogen species; NGF-neurotrophic growth factor; VEGF-vascular endothelial growth factor. Created with BioRender.com.

malignant transformation of MC.[27,28] Malignant cells attract myeloid-derived supressor cells (MDSCs), tumor associated macrophages (TAMs), and regulatory lymphocytes (Treg). These cells potentiate tumor development and promote immune escape, extracellular matrix remodeling, and angiogenesis[29,30] (Figure 1).

Tumor necrosis factor-alpha (TNFA) and nuclear factor-kB (NF-kB) signaling were also involved in MC response to asbestos. Crocidolite causes the accumulation of macrophages in the pleura and lung, which, in turn, release TNFA. Crocidolite also induces MC to express the TNFA receptor, TNF-R1, as well as to secrete TNFA (thus causing paracrine and autocrine responses).[31] The activation of the NF-kB pathway by TNFA allows MCs bearing asbestos-induced DNA damage to eventually evolve into MM. In fact, by causing the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS), whose production is catalyzed by iron, asbestos fibers can induce genotoxicity indirectly, which may lead to a wide spectrum of mutations.[32] Therefore, part of the pathogenetic mechanism of asbestos fibers is thought to be associated with their persistence in the pleura over long periods of time triggering repeated cycles of lesion/repair at the inflammation site.[33-35] Indeed, the presence of inflammatory cells in the tumor is a prognostic factor[26,36-39] (Figure 1).

MPM CLINICAL PRESENTATION, DIAGNOSIS, AND CLASSIFICATION

The latency period between the first exposure to asbestos and the diagnosis of MM is about 30 years. The unavailability of an effective screening method to detect the disease at an early stage hampers its diagnosis.[40] In turn, the diagnosis is followed by survival ranges between 12 and 30 months for localized disease, and between 8 and 14 months in advanced disease.[41,42] Most newly diagnosed patients have advanced disease, and first-line therapy prolongs survival by an average of about three months.[8,43]

The most common clinical manifestation of MPM is progressive dyspnea, usually secondary to pleural effusion formation, associated or not with non-pleuritic chest pain caused by chest wall invasion. Non-productive cough, fever, asthenia, hypoxia, weight loss, or night sweats may also be present. The disease is usually unilateral (95%) and predominantly localized to the right hemithorax (60%). Symptoms usually manifest insidiously and for a long period of time from the initial presentation to diagnosis (3 to 6 months), eventually leading to diagnosis at an advanced stage.[14,43]

Diagnosis depends on the integration of clinical presentation, imaging, and pathology. Specifically, pleural effusion appears on physical examination or chest radiography in up to 95% of cases, but its volume decreases with disease progression. The presence of chest pain or a palpable mass suggests invasion of the chest wall and portends surgical inoperability. Thoracic tomography, as well as thoracic magnetic resonance imaging, allows visualization of pleural effusion, the presence of pleural masses, and assessment of the hilar and mediastinal lymph nodes. However, magnetic resonance imaging is a more sensitive method and should be considered in potentially resectable cases.[43] In turn, PET-CT (positron emission tomography-computed tomography) is useful for detecting lymph node involvement, contralateral thoracic involvement, and distant metastases.[14,44] Figure 2 shows representative images of MPM.

The 2015 classification of WHO divides MM into epithelioid (60-80%), biphasic (10-15%), and sarcomatoid subtypes (10%), with desmoplastic (2%) features recognized in the sarcomatoid subtype. In some cases, classification can be difficult due to the presence of mixed populations.[45,46]

Epithelioid mesotheliomas have architectural, cytologic, and stromal features that allow a variety of differential diagnoses with other neoplasms. In epithelioid mesotheliomas, nuclear atypia and necrosis are independent prognostic factors, allowing the classification of epithelioid mesotheliomas into low and high histologic grades (Figure 3).[47,48]

In sarcomatoid mesotheliomas, the cells are spindly and distributed in fascicles or in a disorganized architectural arrangement, showing mild to severe cytologic atypia, in addition to the possibily of having heterologous elements. Biphasic mesothelioma must contain at least 10% of epithelioid and sarcomatoid components each, whereas desmoplastic mesothelioma must have at least 50% hyalinized fibrous stroma. Patients with sarcomatoid and biphasic tumors have significantly worse survival than those with epithelioid mesothelioma.[49]

Pleural fluid cytology allows MPM diagnosis in up to 1/3 of cases. However, the diagnosis is limited to epithelioid subtype because the sarcomatoid variant does not desquamate into the pleural space. Fine needle aspiration biopsy (FNAB) provides an accuracy of approximately 30%.[50] Unguided pleural biopsy increases the accuracy of FNAB; however, computed tomography-guided pleural biopsy is more sensitive and can establish the diagnosis in ~87% of the cases.[43] The use of video-assisted thoracoscopy/pleuroscopy has an accuracy ≥95% and is the ideal diagnostic method.[51]

Histopathological diagnosis of mesothelial lesions imply significant challenges, including differentiation of malignant lesions from benign tumors and reactive mesothelial hyperplasia or reactive fibrous pleurisy. In pleural biopsies, it can be difficult to differentiate between reactive hyperplastic mesothelium and mesothelioma, as both situations involve cytologic atypia, increased cellularity, and mitosis. Infiltration features, vascular pattern, growth pattern, extent of necrosis, and characteristics of the papillae are

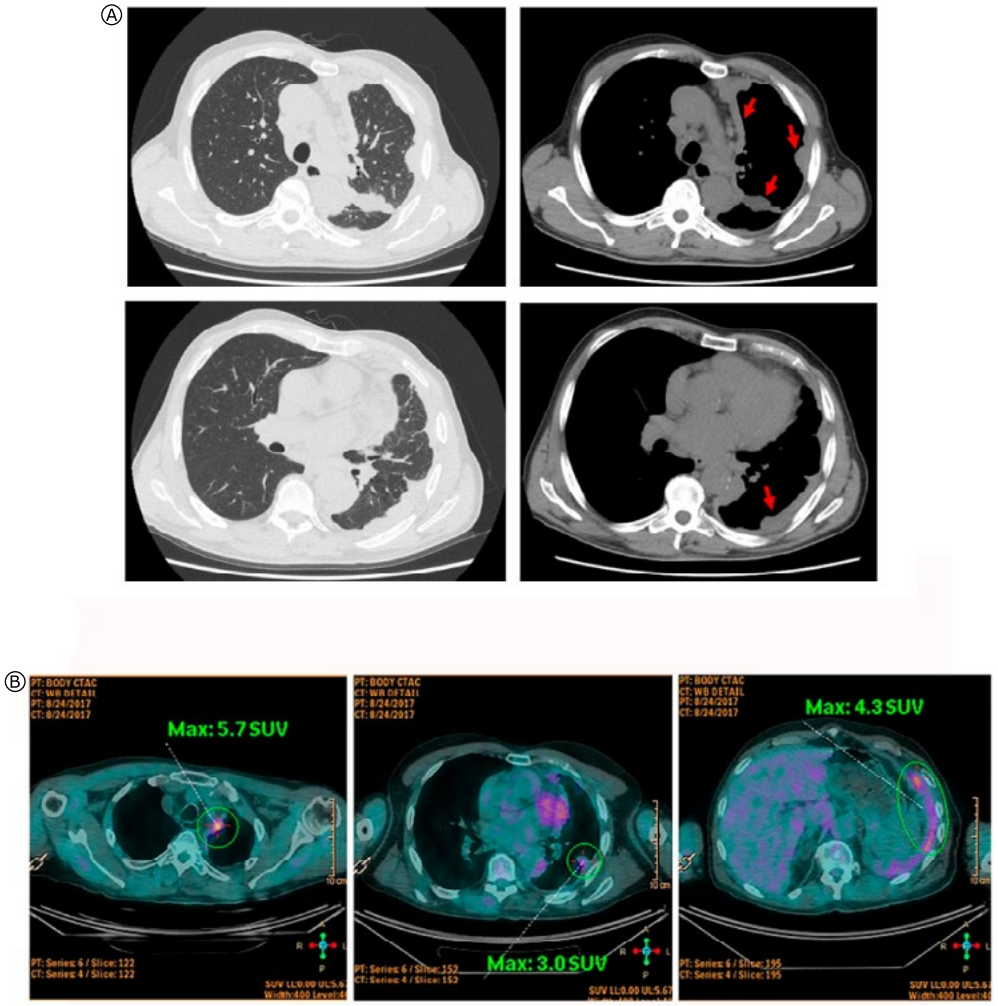

Figure 2. Representative images of the thorax from a male patient diagnosed with biphasic pleural malignant mesothelioma. (A) CT scan showing multiples areas on pleural thickening in the fissure, as well as in mediastinal and parietal pleura, sometimes forming pleural nodules, can be seen in the left hemithorax (red small arrows); (B) 18-FDG PET-CT scan showing various areas of hypermetabolic (glucose avid) tissue in the pleura can be observed on the left hemithorax.

important criteria that cannot always be evaluated in biopsies. Recently, loss of BAP1 (BRCA1-associated protein-1) expression by IHC, homozygous deletion of CDKN2A (p16) by FISH, and expression of methylthio-adenosine phosphorylase (MTAP) by IHC were added as markers to distinguish non-neoplastic from neoplastic cells when mesothelial proliferation is confined to the serosal surface. This may contribute to the differential diagnosis of reactive mesothelial hyperplasia and *in situ* malignant mesothelioma, as well as reactive mesothelial proliferations (pleurisy) that may extend to the stroma and simulate infiltrative mesothelioma.[52,53] Nuclear expression of the BAP1 protein is preserved in reactive mesothelial cells. In epithelioid mesothelioma, complete loss of expression of BAP1 and deletion of *CDKN2A* are present in up to 70% of cases.[50]

This is complicated because the MPM morphologic patterns can simulate a variety of epithelial and nonepithelial malignancies, including carcinomas, sarcomas, melanomas, lymphomas, among others.[50] Immunohistochemistry (IHC) is crucial to differentiate these entities.[52] However, no single IHC marker is sufficiently sensitive or specific to identify MPM; therefore, the use of panels consisting of at least two carcinoma markers (e.g., pCEA BER -EP4, MOC -31, Claudin 4, HEG1) and two mesothelial markers (i.e., WT1, calretinin, CK5/6, D2-40) is recommended[45,50] (Table 1).

Pleural adenomatoid tumor presents as a solitary, noninfiltrative nodule, which may contribute to the differential diagnosis with adenomatoid/microcystic mesothelioma. Somatic mutation of *TRAF7* and preservation of BAP1 favor the diagnosis of an adenomatoid tumor.[55]

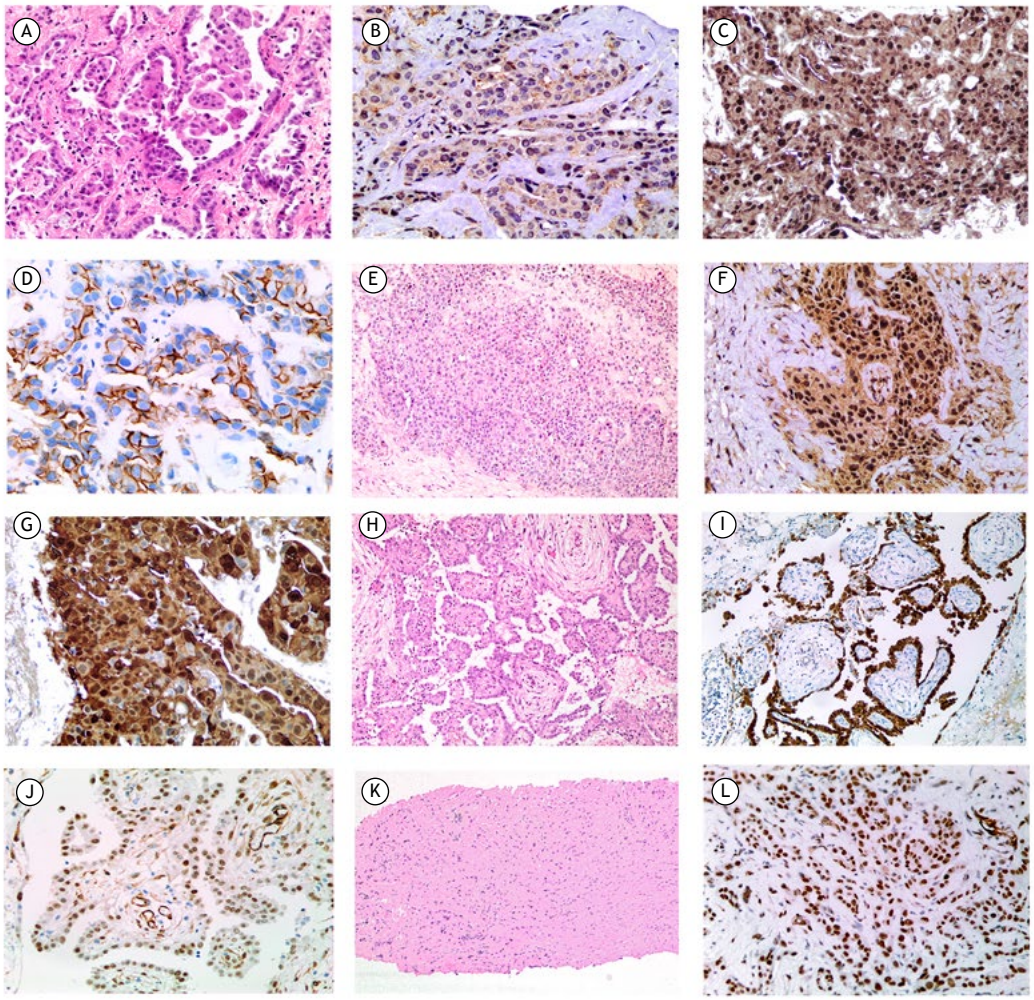

Figure 3. Photomicrographs of MPM. (A-D) epithelioid mesothelioma. (A) H&E staining showing atypical mesothelial cells arranged in papillary and tubulo-glandular patterns amid loose connective tissue. 200x; (B) loss of BAP1 expression in the nucleus of tumor cells, DAB IHC, 200x; (C) calretinin expression in tumor cells cytoplasm, DAB IHC, 200x; (D) D2-40 expression in tumor cells membranes; (E-G) Pleomorphic/solid epithelioid MPM; (E) H&E staining, 100x; (F) BAP1 expression in the nucleus of tumor cells, DAB IHC, 200x; (G) calretinin expression in tumor cells cytoplasm; (H-J) Papillary MPM. H) H&E staining showing a monolayer of mesothelial cells with low grade nuclear atypia covering a fibrovascular core, 100x; (I) calretinin expression in the nucleus and cytoplasm of tumor cells, DAB IHC, 100x; (J) WT1 expression in the nucleus of tumor cells, DAB IHC, 200x; (K-L) Desmoplastic MPM; (K) H&E staining showing isolated round and spindled mesothelial cells amidst a dense desmoplastic stroma, 40x; (L) WT1 expression in the nucleus of tumor cells., DAB IHC, 200x. DAB- 3,3'-diamino-benzidine. H&E- hematoxylin and eosin. IHC-immunohistochemistry.

Table 1. Immunohistochemical markers for diagnosis and differentiation of MM.

Mesothelial markers	Sensitivity	Specificity *versus* Lung adenocarcinoma
Calretinin	> 90%	90-95%
CK5/6	75-100%	80-90%
WT1	70-95%	~100%
D2-40	90-100%	85%
Adenocarcinoma (epithelial markers)	**Sensitivity**	**Specificity *versus* Malignant mesothelioma**
MOC31	95-100%	85-98%
BerEP4	95-100%	74-87%
BG8 (Lewis Y)	90-100%	93-97%
B72.3	25-85%	> 95%

Source: Henderson et al.[54]

For the diagnosis of metastatic carcinomas, it is recommended to add specific antibodies for primary sites, such as lung adenocarcinomas (TTF-1, napsin A), squamous cell carcinomas (p63, p40), renal cell carcinomas (PAX-8, CAIX), colorectal adenocarcinomas (CDX2), and prostate adenocarcinomas (PSA, NKX.3), in addition to the IHC panel described above. The GATA-3 antibody expressed in breast carcinomas and urothelial carcinomas may also be positive in mesotheliomas. Metastatic melanomas will express S-100, Melan-A, HMB-45, and SOX-10. Epithelioid vascular tumors (hemangioendothelioma and angiosarcoma) express CD34, CD31, and ERG, which are usually absent in mesotheliomas. A solitary pleural tumor may mimic sarcomatoid mesothelioma, nevertheless, they satin for STAT6 and CD34, and bear *NAB2-STAT6* gene fusion. In the differential diagnosis of sarcomatoid and biphasic mesothelioma with synovial sarcoma (monophasic and biphasic), molecular testing is recommended to look for *SYT-SSX1* or *SYT-SSX2* fusions, as both have nuclear labeling for TLE1. It can be challenging to establish a differential IHC diagnosis between sarcomatoid mesothelioma and primary sarcoma of the chest wall or metastases of sarcoma to the pleura, especially when heterologous components are present in the mesothelioma.[50,56] Figure 3 shows representative photomicrographs of MPM.

MOLECULAR PATHWAYS OF MM

Genomic alterations

Understanding the molecular mechanisms associated with the development of MM (Table 2) began with conventional cytogenetics and comparative genomic hybridization (CGH) analyses, which showed numerical alterations in all chromosomes, indicating that losses were more common than gains.[85,86] These studies have revealed a complex pattern of chromosomal aberrations in MPM and suggest that gene copy number alterations (CNA) are a major mechanism of carcinogenesis in this disease.[87] Multiple sites of chromosomal loss have been observed in 1p, 3p, 4, 6q, 9p, 11q, 13q, 14q, 15q, 17p, 18q, and 22q,[64,65,86,87] suggesting the involvement of tumor suppressor genes in deleted regions. Although less common, chromosomal gains of 5p, 7p, 8q, 12p, 17q, and 18q have also been documented.[88]

Commonly deleted loci include those containing tumor suppressors *CDKN2A* (cyclin-dependent kinase inhibitor 2A), located on 9p21.3,[57] *NF2* (neurofibromin 2), on 22q12,[59,60] *BAP1*(BRCA1-associated protein-1), located on 3p21.3,[67,89] and *TP53*, on 17p13. CDKN2A, encoding p16-INK4 and ARF, is the most frequently inactivated tumor suppressor gene in MM, with an incidence of homozygous deletion of 50%.[57,58,77] Loss of *CDKN2A* is associated with nonepithelial histology[90] and poorer survival.[64,91,92] *NF2* encodes the protein Merlin,[59] a transcriptional co-activator associated with ubiquitin ligase complexes and the Hippo pathway.[93,94]

Approximately 20-40% of MM have deletions or mutations in *BAP1*[67,77,78][67,77,78] and germline mutations in this gene increase the risk of mesothelioma development.[89] In mouse models, inactivation of only one *BAP1* allele increases asbestos tumorigenicity.[89] *TP53* mutations are present in approximately 8% of MM. Although this incidence is much lower than in other tumor types,[77] it is important to emphasize that *CDKN2A*, which encodes ARF and reduces MDM2 expression, is often lost. Therefore, deletion of CDKN2A results in an increase in MDM2 expression, which triggers ubiquitination and degradation of p53.[95,96] Thus, the phenotype of decreased p53 expression due to *CDKN2A* is similar to that of *TP53* mutation. Indeed, animal models heterozygous for *TP53* develop MM more rapidly when exposed to asbestos.[97]

No oncogene has yet been identified in MM, suggesting that MM is a malignancy resulting from inhibition of tumor suppressors rather than transformation by activation of oncogenes.[98]

The advancement of next-generation sequencing allowed several groups to provide a comprehensive analysis of molecular alterations in MM, which not only confirmed the previously found CNA but showed that the same genes also have common point mutations.[69,99,100]

Bueno et al.[77] published an analysis of 95 MM that confirmed previous findings of tumor suppressor genes CNAs (e.g., *BAP1, NF2, CDKN2B*, and *TP53*). In addition, newly identified mutations were described in genes that include histone modifiers such as *SETD2, SETDB1*, and *SETD5*, members of the RNA helicase family *DDX3X* and *DDX51*, a target of negative mTOR regulation *ULK2*, and a calcium channel component *RYR2*.

In another landmark study of 74 MM samples, TCGA reported deletion of *CDKN2A* and loss of *NF2* by deletion or mutation. *CDKN2A* deletions often encompass *MTAP*, which encodes methylthioadenosine phosphorylase.[81] Loss of *CDKN2A* was strongly associated with shorter overall survival and non-epithelioid histology.[64,90-92]

Two studies, involving 42 patients[73], and a larger cohort of 266 patients[84] employed targeted sequencing of key mutant MPM genes (including *BAP1, NF2, TP53, SETD2, LATS2*, and the *TERT* promoter). A molecular classification into epithelioid and sarcomatoid groups was proposed, with *BAP1* alterations found preferentially in the epithelioid group, whereas alterations in *TP53* and *LATS2* were mostly present among the sarcomatoid subtype.[84]

In addition to the highly consistent alterations in tumor suppressor genes, rarer genetic alterations have also been described. For example, activating mutations in the canonical MAPK or PI3K/AKT pathways were reported in two cohorts,[70,101] but were not identified in the TCGA cohort.[81] Recurrent novel amplification of *RASSF7* was observed in a series of 121 patients and, together with alterations in other genes from the Hippo pathway (*NF2, LATS1,* and *LATS2*), suggests a significant contribution of this pathway to tumorigenic processes.[83]

Table 2. Genomic alterations associated with MM.

Ref	Number of cases/ samples	Techniques used	Main findings
Cheng et al.[57]	40 cell lines and 23 primary tumors	Southern Blot and Targeted Seq of p16	Homozygous deletions on p16-INK in 85% both cell lines and 23% of tumors
Xio et al.[58]	50 primary tumors	FISH for p15 and p16.	Co-deletion of p15 and p16 in 72% of cases.
Sekido et al.[59]	14 cell lines and 10 primary tumors	SSCP and Southern Blot for NF2	*NF2* mutations in 41% of cases.
Bianchi et al.[60]	15 cell lines and 7 primary tumors	SSCP; Targeted Seq for NF2	*NF2* mutations in 53% of cases.
Björkqvist et al.[61]	34 primary tumors	CGH array; Southern Blot.	loss in 4q, 6q and 14q and gain in 15q and 7p
Prins et al.[62]	12 cell lines	PCR; FISH	Chromosome 9 deletion including *CDKN2A* but not *CDKN2B*.
Taniguchi et al.[63]	17 primary tumors and 9 cell lines	CGH array; Southern Blot; Targeted Seq of NF2;	Gains in 1q, 5p, 7p, 8q24 and 20p; Loss in 1p36.33, 1p36.1, 1p21.3, 3p21.3, 4q22, 6q25, 9p21.3, 10p, 13q33.2, 14q32.13, 18q and 22q.
Ivanov et al.[64]	22 primary tumors	CNA array	Deletions in 22q12.2, 19q13.32 and 17p13.1 in 55-74% and gain in 5p, 18q, 8q and 17q in 23-55% of cases.
Cheung et al.[65]	22 cell lines	CNA array	deletions of CDKN2A/ARF and CDKN2B, 1p36, 1p22, 3p21-22, 4q13-34, 11q23, 13q12-13, 14q32, 15q15, 18q12 and 22q12 in 55-90%
Takeda et al.[66]	40 primary tumors	9p21 FISH	9p21 deletion in 35 of 40 cases (88%)
Bott et al.[67]	53 primary tumors	CGH array, FISH; Targeted Seq.	Deletions at 9p21, 22q and 3p21. Mutations in BAP1, NF2, LATS1
Yoshikawa et al. [68]	23 primary tumors	Targeted Seq of BAP1	biallelic BAP1 gene alterations in 14 of 23 MMs (61%)
Guo et al.[69]	22 primary tumors	Whole-exome Seq	Major changes in copy numbers: *BAP1*, *NF2*, *CDKN2A*, *CUL1*.
Lo Iacono et al.[70]	123 primary tumors	Targeted NGS of 52 genes	Alterations in p53/DNA repair (TP53, SMACB1, and BAP1) and PI3K-AKT pathways (PDGFRA, KIT, KDR, HRAS, PIK3CA, STK11, and NF2).
Nasu et al.[71]	22 primary tumors	Targeted BAP1 Sanger Seq.; MLPA	alteration of BAP1 in 63.6% of cases
Borczuk et al.[72]	48 peritoneal and 41 pleural tumors	CNA array	Loss in BAP1, CDKN2A and NF2 in both tumor sites. Copy number gain were more common in peritoneum, loss were more common in pleura
Kato et al.[73]	42 primary tumors	Targeted NGS of 236 genes	Alterations in *BAP1* (47,6%), *NF2* (38,1%) and *CDKN2A/B* (35,7%).
Kang et al.[74]	78 primary tumors	Targeted Seq of SETDB1	Mutations in 7 patients
Ugurluer et al.[75]	11 primary tumors	Targeted NGS of 236 mutations	Mutations in 86% of pleural and 50% of peritoneal cases. Most mutated genes were BAP1 (36%), CDKNA2A/B (27%) and NF2 (27%).
Chirac et al.[76]	33 peritoneal primary tumors	CGH array	Genomic pattern similar to pleural mesothelioma: loss of 3p21, 9p21, and 22q12. novel CNA included 15q26.2 and 8p11.22

Table 2. Continued...

Ref	Number of cases/ samples	Techniques used	Main findings
Bueno et al.[77]	216 primary tumors	Whole Exome Seq, Targeted NGS	BAP1, NF2, TP53, SETD2, DDX3X, ULK2, RYR2, CFAP45, SETDB1 and DDX51 significantly mutated genes. Gene fusion and splice alterations in NF2, BAP1 and SETD2. Alterations in Hippo, mTOR, histone methylation, RNA helicase and p53 signaling pathways.
Yoshikawa et al.[78]	33 primary tumors	CGH array for the 3p21 region; Targeted NGS of 4 genes	biallelic gene inactivation in SETD2 (9 of 33, 27%), BAP1 (16 of 33, 48%), PBRM1 (5 of 33, 15%), and SMARCC1 (2 of 33, 6%)
Desmeules et al.[79]	25 primary tumors	FISH	Identification of a *EWSR1/ FUS-ATF1* gene fusion in 4 cases
Hung et al.[80]	88 peritoneal primary tumors	FISH; Targeted NGS for ALK	ALK rearrangements in 3 cases with ATG16L1, STRN, and TPM1
Kim et al.[9]	13 peritoneal primary tumors	Targeted NGS of 510 genes;	Bi-allelic inactivation of BAP1 (9/13 cases), mutation in *NF2 (3/13)*; *SETD2 (2/13)* e *DDX3X (2/13)*.
Hmeljak et al.[81]	74 primary tumors	Whole Exome Seq.; CNA array	Inactivating alterations by mutation and CNA in: BAP1, CDKN2A, NF2, TP53, LATS2, and SETD2. Novel molecular subtype (3% of cases) genomic near-haploidization and TP53 and SETDB1 mutations
Hassan et al.[82]	239 genomic DNA from MM patients	Targeted NGS of 73 genes	12% of cases had germline mutations: 16 in BAP1 and 12 distributed among CHEK2, PALB2, BRCA2, MLH1, POT1, TP53, and MRE11A
Nastase et al.[83]	121 primary tumors	CNA array, Whole Exome Seq.;	CDKN2A deletion in 60% of tumours; BAP1 mutated or deleted in 54%; RASSF7 amplification in 33%; RB1 deleted or mutated in 26%; NF2 mutated in 20%; TP53 mutated in 8%; SETD2 in 6%; DDX3X in 5% and LATS2 in 5%.
Quetel et al.[84]	266 primary tumors	Targeted NGS 21 genes	TERT promoter, *NF2*, and *TP53* mutations associated w/ worse survival.

BAP1

Although the risk of developing MM is much higher among workers of the asbestos industry,[102] not all exposed workers develop the disease. This prompted to the search for genetic factors that predispose to MM, especially in families with multiple affected individuals,[103] which led to the identification of *BAP1* gene role.

BAP1 is an enzyme of the c-terminal hydrolase family with pleiotropic activities found in DNA repair complexes associated with BRCA1 and functions as a de-ubiquitinase.[104-106] Expression of BAP1 is associated with reduced tumor growth in several experimental models and interacts with cell cycle regulatory proteins.[107] In addition, BAP1 forms several nuclear complexes that can regulate gene transcription. Therefore, BAP1 is expected to affect a variety of cellular functions, such as chromatin remodeling, cell cycle progression, cell differentiation, and DNA repair. The BAP1 protein is also known to play an important role as an apoptosis inhibitor caused by metabolic stress.[108]

Deletions or mutations in BAP1 have been described in approximately 60% of MM,[67,68,70,71,77,78,81] with nearly 85% of peritoneal tumors having BAP1 alterations, comparing with only 20-30% of pleural tumors.[109] BAP1 is also consistently inactivated in

clear cell renal carcinomas, uveal melanomas, and cholangiocarcinomas.[110] Most mutations in BAP1 are frameshift or missense, resulting in loss of protein expression.[67,77,78] Accordingly, loss of BAP1 protein expression can be identified by immunostaining of tumor tissue, which is observed in approximately 60% of the cases.[71] Loss of protein expression is observed in approximately 60% of the cases.[111] Despite its high prevalence, loss of BAP1 expression has not been shown to affect overall survival,[71] but has been indicated to affect response to chemotherapy.[107]

Point mutations are also present in *BAP1* and can lead to amino acid substitution, whose effect on protein activity is not always obvious. For example, mutations I47F, F81V, A95D, and G178V lead to loss of protein stability and amyloid aggregation.[112] On the other hand, mutations such as A95D, Y724X, and 10 F679LfsX37 lead to a change in subcellular location from nuclear to cytoplasmic.[113]

Germline mutations in *BAP1* are associated with a highly penetrant syndrome of MM. The so-called BAP1 tumor predisposition syndrome (BAP1-TPDS) was identified by three independent research groups investigating MM, cutaneous melanoma, and uveal melanoma. Later, other tumor types such as cholangiocarcinoma, clear cell renal carcinoma, basal cell carcinoma, lung cancer, breast/ovarian carcinoma, meningioma, neuroendocrine tumors, and some types of sarcomas were added to the syndrome spectrum.[89,114] However, the molecular mechanisms involved in these specific tumor types and in disease progression are not understood. Like other tumor suppressor genes, germline mutations in *BAP1* are inherited in an autosomal dominant manner. Although penetrance is incomplete and tumor may vary in different members of the same family, more than 80% of gene carriers are affected by at least one type of cancer.[115]

MPM is the second most common tumor identified in BAP1-TPDS, comprising 22% of tumors. Comparing with sporadic MPM, the median age of onset in germline-associated MPM is significantly earlier (74 and 46 years, respectively),[111] and survival rates are 7-fold longer.[116]

Despite the high relevance of germline mutations in *BAP1* in higher risk of developing hereditary MM and other tumors of the syndrome, a significant proportion of families with multiple mesothelioma cases do not have mutations in this gene, suggesting that other genes may predispose to these tumors.[117,118] Along this line, a recent study examined 94 hereditary cancer predisposition genes in 93 mesothelioma patients and detected likely pathogenic mutations in 10% of the cases, with an enrichment of mutations in genes of the homologous recombination DNA repair pathway. Interestingly, patients with mutations in these genes reported exposure to asbestos less frequently.[118]

Gene expression profile

Genetic alterations leading to phenotypic disorders produce altered gene expression profiles, knowledge of which may improve our understanding of relevant molecular pathways. Early studies using gene expression profiling in MM suggested the existence of two relevant molecular subtypes associated with histological classification: epithelioid and sarcomatoid.[119-121] Interestingly, genes associated with epithelioid-mesenchymal transition (EMT) were enriched in the sarcomatoid group, indicating a more mesenchymal phenotype.[121] Further work suggested that 4 subtypes can be distinguished and are associated with the spectrum from epithelioid to sarcomatoid histology, confirming the differential expression of EMT genes.[77,81] This was corroborated through data reanalysis, which showed that the molecular groups represent a continuum or histo-molecular gradient in which tumors can be dissected into a combination of epithelioid-like (E-score) and sarcomatoid-like (S-score) signatures, whose proportions are associated with prognosis.[122]

MPM TREATMENT

Prognostic factors

Established prognostic indicators, such as histologic subtype, age, and sex, can provide some information to predict patient survival, but there are few definitive and specific prognostic indicators routinely used to predict likely outcomes in individual patients. The European Organization for Research and Treatment of Cancer (EORTC) suggests that poor performance status, leukocytosis, sarcomatoid type, and male individuals are associated with poorer prognosis.[123] Meanwhile, the CALGB score includes age of 75 years, non-epithelioid histology, LDH 500UI/L, pleural involvement, platelets 400,000/mm3, chest pain, and poor PS as unfavorable prognostic factors.[124] Other prognostic indices include weight loss, hemoglobin, and serum albumin levels,[125] or WBC.[126]

In addition to its involvement in pathogenesis, systemic inflammation is associated with overall survival and response to treatment. Prognostic factors based on inflammatory response, which include the combination of C-reactive protein and albumin, the combination of neutrophil and lymphocyte counts (neutrophil-to-lymphocyte ratio, NLR), and the combination of platelet and lymphocyte counts are associated with survival in patients with various cancers, including MPM, with higher levels predicting poorer survival.[39]

Surgery

In the setting of resectable disease, treatment of MPM is based on trimodal therapy: surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy, especially in patients without lymph node involvement.[127]

Generally, prognosis is dismal, as most patients have unresectable disease at diagnosis or are considered inoperable due to age, performance status, or comorbidities. It is important for patients who are candidates for surgery to undergo EBUS (endobronchial ultrasound) or mediastinoscopy, as mediastinal lymph node dissemination is a poor prognostic factor in MPM.[14]

For resectable tumors, the three most commonly used surgical procedures in the treatment of mesothelioma are thoracoscopy with pleurodesis, pleurectomy/decortication, and extrapleural pneumonectomy.[43]

Pleurectomy/decortication is a surgical procedure aimed at reducing tumor burden. This procedure is performed through open thoracotomy and consists of removing the parietal pleura, including the portion adjacent to the mediastinum, pericardium, and diaphragm (often requiring removing a portion of the diaphragm), and removal of the visceral pleura to decorticate the lung. This treatment provides relief of local symptoms and prevents recurrence of pleural effusion, but usually implies a high rate of locoregional (80% to 90%) or distant recurrence (10% to 36%), in addition to being usually not curative.[43]

However, the role of pleurectomy/decortication is debatable. The MesoVATS trial compared talc pleurodesis with video-assisted thoracoscopic partial pleurectomy (VAT -PP). VAT-PP did not result in a better OS (HR =1.04; 95%CI 0.76-1.42; p=0.81) and had a higher rate of surgical complications (31% x 14%, p=0.019); in addition, quality of life at 6 months was better in the VAT -PP group.[128]

Extrapleural pneumonectomy (EPP) is considered a more aggressive technique for involving "*en bloc*" removal of tissue in the hemithorax, including visceral and parietal pleura, affected lung, mediastinal lymph nodes, diaphragm, and pericardium. It is not usually considered in patients with limiting comorbidities, low performance status, mediastinal lymph node involvement, or sarcomatoid histology because of the morbidity and mortality and poorer prognosis among these patients.[129]

Pleurodesis is a procedure to remove fluid accumulation in the pleural space. It involves drainage of the fluid through thoracoscopy under general anesthesia or sedation or by inserting a thoracic tube through thoracostomy. After removing the fluid, sclerosing chemicals are introduced into the pleural cavity to prevent the fluid from accumulating again.[130]

A comparison between extrapleural pneumonectomy or pleurectomy/decortication in 663 patients revealed significant differences in survival, with a 1.4-fold higher risk of death for extrapleural pneumonectomy (p=0.001), after controlling for disease stage, histology, gender, and multimodality therapy.[131] In another randomized controlled trial, patients receiving platinum-based neoadjuvant chemotherapy were randomized to extrapleural pneumonectomy or not. No survival or quality-of-life differences were observed between the groups.[132]

Radiotherapy

The main current indications for radiotherapy in MPM are: hemithoracic radiotherapy before or after extrapleural pneumonectomy, hemithoracic radiotherapy after decortication/pleurectomy, and palliative radiotherapy to relieve local symptoms.[133]

Radical hemithoracic radiotherapy (RHR) can be performed after extrapleural pneumonectomy to improve local control, although it is associated with in-field failure rates of 15% to 35%.[134] Although the topic is still debated, several treatment guidelines recommend RHR, such as the NCCN (National Comprehensive Cancer Center).

The SAKK 17/04 trial,[135] a prospective phase II, investigated the role of adjuvant RHR after platinum-based neoadjuvant chemotherapy followed by extrapleural pneumonectomy. Patients were randomized to radiotherapy vs observation. There was no significant difference between the groups. More recently, a phase III study compared RHR with palliative radiotherapy after non-radical lung sparing surgery and chemotherapy, reaching better OS in the RHR arm (2-year OS 58% x 28%; HR 0.58, 95CI 0.31-0.95, p=0.031), at the cost of higher grade 3/4 toxicity.[136]

The rationale for the use of neoadjuvant hemithoracic radiotherapy prior to extrapleural pneumonectomy arose from observing a frequent tumor spread to the contralateral lung and peritoneum, which may be related to surgery. The SMART (Surgery for Mesothelioma After Radiation Therapy) strategy[137] was developed to achieve lower spread rates associated with surgical intervention. The authors observed a median overall survival of 51 months and a median disease-free survival of 47 months for epithelioid pleural mesothelioma, suggesting such strategy to provide some benefit to this population.

Following the publication of controversial data from the MARS-1 study, the use of extrapleural pneumectomy has declined in recent years in favor of lung-sparing techniques, such as pleurectomy and lung decortication. The IMPRINT study, a prospective phase II trial, demonstrated the safety of delivering intensity-modulated radiotherapy to the hemithorax concurrently with chemotherapy in patients who had undergone pleurectomy and lung decortication.[138]

In the palliative context, radiotherapy can be used to control a range of symptoms for which drug treatment is sometimes inadequate, such as chest pain associated with chest wall invasion, hemoptysis, cough or dyspnea, as well as to prevent spinal cord compression.[139]

Systemic treatment

Systemic chemotherapy is the treatment of choice in the setting of unresectable disease and for patients with relapsed disease or that do not wish to have surgery[9] (Figure 4). In first-line chemotherapy, regimens containing platinum have higher response rates than platinum-free regimens.[140] Pemetrexed-based regimens have been the first-line systemic chemotherapy option in most institutions, although no consensus has been reached on which agent(s) should be used to supplement pemetrexed.[9] Substituting cisplatin with carboplatin resulted in an ORR of 25-29%, but with better toxicity profile and similar OS.[141]

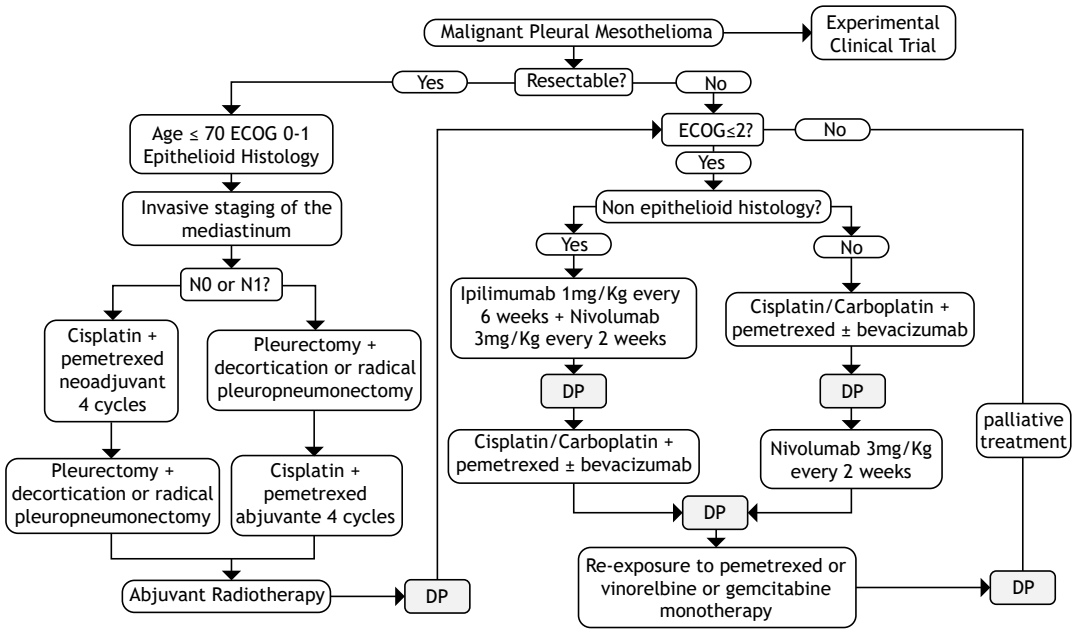

Figure 4. Diagram summarizing current treatment for MPM. It should be highlighted that, if available, all patients must be considered for participation in investigational clinical trials.
DP: disease progression.

The addition of bevacizumab to cisplatin and pemetrexed in the first-line setting improved OS (18.8 months vs. 16.1 months) and progression-free survival (PFS) (9.2 months vs. 7.3 months) compared with cisplatin and pemetrexed in a recent phase III study (MAPS).[142] However, the use of anti-angiogenic drugs in combination with chemotherapy is not widespread, as other trials testing angiokinase inhibitors, such as cediranib and nintedanib, were negative.[5,143,144] Nevertheless, ramucirumab, an anti-VEGFR-2 antibody, was combined with gemcitabine in a randomized phase II trial (RAMES trial) and compared with gemcitabine as a single agent in second-line MPM not previously treated with antiangiogenic drugs. The combination doubled median OS (7.5 x 13.8 months) and median PFS (3.3 x 6.2 months), although no difference in ORR was observed.[145]

The use of immune checkpoint inhibitors (ICI) has revolutionized the treatment of various tumor types in recent years.[26] Immunotherapy is a treatment modality that explores the patient's immune system to eliminate tumor cells. Examples of immunotherapeutic approaches currently under investigation include inhibitors of T-cell immune checkpoints or agonists of T-cell activation pathways, the use of cytokines such as IL-12 and IL-15, therapeutic vaccines, elimination of immunosuppressive cells, and modulation of other components of the immune response.[146]

CTLA4 is a T cell receptor that plays a key role in preventing T cell hyperactivation.[147] CTLA4 signaling decreases T cell activation and the ability of memory T cells to support an immune response.[148] Greater inhibition of tumor growth was observed upon administering anti-CTLA4 monoclonal antibody between cycles of cisplatin in mesothelioma mouse models.[149] Furthermore, CTLA4 blockade alternating with cisplatin treatment inhibited tumor cell proliferation while increasing the number of T lymphocytes infiltrating the tumor. Despite these results, DETERMINE, a multicenter, randomized, placebo-controlled phase IIB trial, failed to show any improvement in OS with the use of tremelimumab (an anti-CTLA4 antibody) in relation to placebo in second- and third-line[150] (Table 3).

PD1 is also an immune checkpoint and has two ligands: PD -L1 and PD -L2. Overexpression of the PD1 receptor plays a key role in T cell exhaustion and is an important factor during the normal immune response in preventing the onset of autoimmunity.[158] PD-L1 is highly expressed in MPM.[159] Positive PD-L1 expression was reported in 40% of 106 mesothelioma specimens, 21% in the epithelioid subtype, 94% in the sarcomatoid subtype, and 57% in the biphasic subtype.[160] Some studies reported worse survival rates in cases of MM with tumor PD-L1 expression,[161,162] whereas others reported no significant difference in survival between cases of MM with and without PD-L1 expression.[163]

Several phase II trials investigated the activity of anti-PD1 antibodies as second-line therapy for pleural mesothelioma and reported an ORR of 9.4-29% and a median PFS of 2.6-6.2 months. Recently, however, a phase III trial (PROMISE-meso) randomized 144 patients with advanced MM who had progressed to previous systemic chemotherapy to receive pembrolizumab or chemotherapy (gemcitabine or vinorelbine). There was no significant difference in PFS (primary endpoint) or OS, but response rate was higher among

Table 3. Trials evaluating immunotherapy in second line for MPM.

Trial	Phase	Arms	N	ORR (%)	PFS median (months)	OS median (months)	PD-L1 Expression
DETERMINE	II	Tremelimumab	569	5	2.8	7.7	NE
KEYNOTE-028[151]	IB	Pembrolizumab	25	20	5.4	18	All tumors were PD-L1+
Kindler et al.[152]	II	Pembrolizumab	35	21	6.2	NR	NA
NivoMes[153]	II	Nivolumab	34	24	2.6	11.8	Trend to higher ORR
MERIT[154]	II	Nivolumab	34	29	6.1	17.3	Improved PFS and OS
JAVELIN[155]	IB	Avelumab	53	9.4	4.3	NR	Trend to improved PFS
NIBIT-MESO-1[156]	II	Tremelimumab + durvalumab	40	25	5.7	16.6	Improved ORR, OS and PFS
INITIATE[157]	II	Nivolumab + ipilimumab	36	29	6.2	NR	Improved ORR
MAPS2	II (randomized)	Nivolumab + ipilimumab Nivolumab	125	28 9	5.6 4.0	15.9 11.9	No association with OS or PFS
PROMISE	III	Pembrolizumab Gemcitabine or Vinorelbine	144	20	2.5 3.4	10.7 12.4	NA
CONFIRM	III	Nivolumab BSC	332	NR	4.2 2.8	9.1 9.7	NA

NE: not evaluated; NA: no association; NR: not reported; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; BSC: best supportive care, N: number of subjects.

patients treated with pembrolizumab (22% x 6%). No association with PD-L1 expression was observed.[164] In contrast, the CONFIRM trial compared nivolumab with placebo in the same scenario and found improved OS (9.2 vs 6.6 months; HR 0.72; 95%CI 0.55-0.94; p=0.02) and PFS (3.0 vs 1.8 months; HR 0.62; 95%CI 0.49-0.78; p 0.001).[165] This suggests that ICIs are active against MM, although not superior to chemotherapy when used in second or further lines.

A French multicenter, randomized, phase II study (MAPS-2) compared nivolumab (anti-PD1) with nivolumab in combination with ipilimumab (anti-CTLA4) in patients who had failed first- or second-line therapy. The 12-week disease control rate was 44% in the nivolumab group and 50% in the combination group. High expression of PD-L1 was associated with a higher response rate.[5] Other phase II studies showed similar results (Table 3).

In the wake of these promising results, the CheckMate-743 trial, a randomized phase III trial, compared the combination of ipilimumab and nivolumab (IO+IO) with cisplatin/carboplatin plus pemetrexed as first-line therapy for unresectable MPM. The study showed a longer OS in the group of patients treated with IO+IO (18.1 x 14.1 months; HR 0.74 95%CI 0.6-0.91; p=0.002). OS at 2 years was 41% and 27% for IO+IO and chemotherapy, respectively. Both histologies benefited from treatment with IO+IO, although the relative improvement was greater in patients with non-epithelioid tumors. CheckMate-743 established this combination as the new standard first-line therapy for metastatic or unresectable MPM.

There is no consensus regarding second-line systemic therapy for advanced pleural mesothelioma, and commonly used drugs are associated with poor response rates and short median survival.[166] Patients who benefited from previous treatment with pemetrexed-containing regimens or who have not been previously exposed to pemetrexed may be treated with pemetrexed,[167,168] otherwise, patients are treated with gemcitabine, vinorelbine, or doxorubicin.[169] Vinorelbine is the only drug directly compared with best supportive care as second-line therapy in advanced MM in a randomized trial (VIM trial) and was associated with improved PFS (median PFS: 4.2 x 2.8 months; HR 0.59; 95%CI 0.41-0.85; one-sided p=0.0017), but had no impact on OS.[165] Figure 4 summarizes the current management of pleural mesothelioma.

More recently, two single-arm phase 2 trials investigated the role of durvalumab in combination with standard platinum- and pemetrexed-based chemotherapy in the first-line treatment of MPM. The first study (PrECOG 0505) showed a median OS of 20.4 months.[170] The OS was 70.4% at 12 months and 44.2% at 24 months. The second study (DREAM) showed a median OS of 18.4 months, a median PFS of 6.7 months, and an ORR of 48%.[171] Given the promising results, a phase III trial will start enrollment soon.

There are several ongoing clinical trials investigating new therapies for MPM (Table 4), and the future is likely to bring new hope for these patients.

Table 4. Ongoing phase III first line treatment trials for Malignant Pleural Mesothelioma.

TITLE	PRIMARY ID	CLINICALTRIALS ID
PHASE III RANDOMIZED TRIAL OF PLEURECTOMY/ DECORTICATION PLUS CHEMOTHERAPY WITH OR WITHOUT ADJUVANT HEMITHORACIC INTENSITY-MODULATED PLEURAL RADIATION THERAPY (IMPRINT) FOR MPM.	NRG-LU006	NCT04158141
RANDOMIZED, DOUBLE-BLIND, PHASE 2/3 STUDY IN SUBJECTS WITH MPM TO ASSESS ADI-PEG 20 WITH PEMETREXED AND CISPLATIN (ATOMIC-MESO PHASE 2/3 STUDY).	POLARIS2015-003	NCT02709512
A PHASE III, RANDOMIZED, OPEN LABEL TRIAL OF NIVOLUMAB IN COMBINATION WITH IPILIMUMAB VERSUS PEMETREXED WITH CISPLATIN OR CARBOPLATIN AS FIRST LINE THERAPY IN UNRESECTABLE MPM	CA209-743	NCT02899299
A MULTICENTRE RANDOMISED PHASE III TRIAL COMPARING ATEZOLIZUMAB PLUS BEVACIZUMAB AND STANDARD CHEMOTHERAPY VERSUS BEVACIZUMAB AND STANDARD CHEMOTHERAPY AS FIRST-LINE TREATMENT FOR ADVANCED MPM.	ETOP 13-18	NCT03762018
A RANDOMIZED, OPEN-LABEL PHASE II/III STUDY WITH DENDRITIC CELLS LOADED WITH ALLOGENEIC TUMOUR CELL LYSATE (PHERALYS) IN SUBJECTS WITH MESOTHELIOMA AS MAINTENANCE TREATMENT (MESOPHER) AFTER CHEMOTHERAPY.	MM04	NCT03610360
A PHASE II/III RANDOMIZED STUDY OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MPM.	IFCT-1901	NCT02784171

CONCLUSION

MPM is largely preventable and global efforts should be made to ban the asbestos industry once and for all. Despite some recent advances, this rare but serious condition still represents an unmet medical need and lacks robust prospective studies to better understand its pathophysiology, as well as randomized trials to define more effective treatments for patients.

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AUTHOR CONTRIBUTIONS

GNMH: final manuscript review and submission, manuscript draft elaboration, literature review, table and graphics construction, conceptualization.

CHC: manuscript draft elaboration, literature review.

CALP: manuscript draft elaboration, literature review, pathological specimens microphotographies.

GV: manuscript draft elaboration, literature review.

JRN: manuscript draft elaboration, literature review.

VCCL: final manuscript review, manuscript draft elaboration, literature review, table and graphics construction, treatment flow chart elaboration, conceptualization, oversight.

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Infectious disease scenarios in a post-vaccine view of COVID-19 and future pandemics

João Paulo Cola[1], Ethel Leonor Noia Maciel[1]

TO THE EDITOR,

In epidemiology of infectious diseases, we study the possible epidemic and endemic scenarios and define, for each disease, the indicators that should be considered to determine when a disease has reached its control, elimination, or eradication.[1]

Control is classically defined as the set of measures, actions, programs, or ongoing activities aimed at reducing the incidence and prevalence of diseases to levels low enough as to be no longer considered a public health issue. The level of control depends on the disease, the availability of resources, and the population's behavior.[1] One example is the monitoring of individuals with respiratory symptoms in the community, an effective measure for detecting cases of tuberculosis (TB), aiming to reduce the transmission of pulmonary tuberculosis and, consequently, minimize the number of cases in the community.[2]

Elimination follows disease control and is achieved when there are no more cases of illness, or they are minimal in number,[1] even though the causes that can potentially produce it persist. For example, TB will be considered eliminated when there is a reduction of 90% in the number of cases and 95% in TB-related deaths by 2035 (compared to 2015); and a low economic impact for families affected by the disease.[2] The WHO has defined the following indicators to consider TB as eliminated in Brazil: decreased incidence of TB cases from 34.3 cases/100 thousand inhabitants in 2015 to 10 cases/100 thousand inhabitants in 2035, and TB-related mortality from 2.3 deaths/100 thousand inhabitants to 1 death/100 thousand inhabitants.

The eradication of a disease is accomplished with the application of population measures aimed at achieving a situation of zero cases or deaths,[1] *i.e.*, one in which not only have the cases of TB been eliminated, but also the causes of the disease, in particular, the microorganism.[1,3] It is important to highlight that the eradication of a disease can only be achieved on a global scale. To date, we have only been able to reach this scenario with the Smallpox virus.

In the case of COVID-19, the world still finds itself in a pandemic situation and far from global control of the disease. In conjunction with the International Science Council,[4] the WHO has been conducting research with a panel of experts to map possible paths ahead and inform decisions that will influence the outcome of the pandemic. Nevertheless, we still have a long way to go. Some researchers[1] debating COVID-19 global control scenarios have suggested two sub-scenarios: cohabitation and conflagration.

In cohabitation, control measures guarantee the prevention of severe forms of the disease but do not ensure the interruption of the transmission chain. As global vaccine coverage advances, viral circulation is reduced, although there is a frequent occurrence of local transmission of the virus, especially in the unvaccinated population. In this aspect, vaccination can provide immunity, but it is necessary to reinforce non-pharmacological measures beyond the vaccine in order to maintain low levels of virus circulation.[1]

In conflagration, on the other hand, the difficulty in accessing vaccines, low vaccination coverage, and the absence of regulated non-pharmacological control measures lead to a scenario characterized by endemic levels of the disease.[1] In this situation, the circulation of the virus with new variants in an unvaccinated population and without effective measures to contain transmission maintains an incidence at moderate to high levels with local transmission of the virus.[5]

In Brazil, we are not yet at the control stage but, depending on vaccine coverage, we can contain the progression of the virus, with the possibility of few variants. It is possible that we could achieve control and remain between conflagration and cohabitation for some time to come. Without a national coordination of control measures for states and municipalities to legislate, and with few non-pharmacological options to contain the virus (based not on reducing transmission, but on minimizing the occupation of intensive care unit beds), it seems that we will undergo a long period of conflagration or cohabitation with COVID-19.

Disease control and even the eradication of COVID-19 with only vaccines requires global population immunity to be able to neutralize possible new variants.[1,3] Vaccines alone are unlikely to end the pandemic. What comes after vaccination advancements depends on government decisions and new scientific evidence. It is possible that the virus will be controlled and eliminated in areas with high vaccination coverage and continued non-pharmacological measures. However, disease control in these areas will depend on the global control of the virus; otherwise, these areas will be constantly vulnerable to cohabitation and conflagration scenarios. It is essential to align science and governance with decisions that reinforce non-pharmacological measures and that are based on evidence that is demonstrated along the way and, consequently, modified.[6]

1. Laboratório de Epidemiologia, Universidade Federal do Espirito Santo, Vitoria (ES), Brasil.

The global community will have to prepare for upcoming pandemics in the future. In Brazil, in a post-pandemic scenario, it will be necessary to build a scientific committee composed of researchers independent from the government that can support actions to be carried out by state and municipal Epidemiological Surveillance Services. Keeping these services active, which were restructured in 2020 to respond to the COVID-19 pandemic, is imperative to achieve advances in the control of diseases and other conditions. Emptying these services post-pandemic will be a fallacy in rapid and effective responses to future epidemics.

AUTHOR CONTRIBUTIONS

JPC and ELNM contributed to the conception and planning of the study, the interpretation of the findings, the writing and revision of the preliminary and final version, and the approval of the final version of the manuscript.

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Use of antifibrotic drugs in familial interstitial pneumonia: analysis of one family

Deborah dos Reis Estrella[1], Eliane Viana Mancuzo[1,2], Ricardo de Amorim Corrêa[1,2]

TO THE EDITOR,

Familial interstitial pneumonia (FIP) is defined as the occurrence of interstitial lung disease (ILD) in two or more individuals within the same family.[1,2] The majority of FIP kindreds present autosomal dominant inheritance with a pattern of incomplete penetrance.[2] The prevalence of idiopathic pulmonary fibrosis (IPF) among patients with FIP is 0.5% - 20.0%; nonetheless, FIP has also been reported in fibrotic hypersensitivity pneumonitis (fHP) and connective tissue disease-associated ILD.[2,3]

Although usual interstitial pneumonia (UIP) is the most prevalent HRCT pattern in FIP, other HRCT and histological patterns within the same family have been reported in 40% - 45% of cases.[1,3] Interstitial lung abnormalities (ILA) have been found in asymptomatic first-degree relatives of patients with FIP, and this pattern of interstitial pneumonia has been associated with a risk of progression to ILD.[2] The appropriate pharmacological treatment of FIP has yet to be defined.[3,4] Here, we describe six cases of FIP within the same family and discuss treatment-related outcomes.

The present case series involved six siblings who were followed up at the Outpatient Clinic for Interstitial Pulmonary Diseases of the Federal University of Minas Gerais' Clinical Hospital, located in the city of Belo Horizonte (MG), Brazil. Data were obtained from medical records and updated through interviews with the patients using a form developed at the clinic. The HRCT scans and histological samples were classified by a radiologist and a pathologist, both with experience in ILD.[5] Pulmonary function tests (PFTs) were performed in accordance with current recommendations.[6] All participants gave written informed consent. This study was part of a research project approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE no. 44843215.5.0000.5149).

Among 17 siblings from the same family, eight were diagnosed with ILD, two of whom died before the beginning of this study. The characteristics of the six remaining siblings with ILD are detailed in Table 1. In five of them, ILD was identified only after the onset of symptoms, when their lung function was already impaired.

In accordance with the current classification,[5] the HRCT patterns found included "UIP" (n = 2), "probable UIP" (n = 2), "consistent with other diagnoses" (n = 1), and "indeterminate for UIP" (n = 1). One of the patients with a "probable UIP" HRCT pattern and another with "consistent with other diagnoses" underwent surgical lung biopsy. The patient with a "probable UIP" HRCT pattern had "UIP" confirmed by histology and, therefore, presented the IPF phenotype. The patient with an HRCT pattern "consistent with other diagnoses" exhibited a histological pattern of "airway-centered interstitial fibrosis", with fHP as the phenotype. The other participant with a "probable UIP" pattern did not undergo lung biopsy because he was diagnosed after his three affected siblings, having ruled out exposure to airborne antigens and connective tissue disease-associated ILD. Thus, he was considered as having FIP with the IPF phenotype. The patient with the "indeterminate for UIP" pattern has been stable regarding clinical, functional, and tomographic findings and, therefore, was not submitted to biopsy. At diagnosis, the spirometry results showed some degree of restrictive lung disease in five of the six patients.

Of the six patients evaluated, five have been treated with antifibrotic drugs, with the exception of the patient with the "indeterminate for UIP" HRCT pattern. Among the five patients undergoing antifibrotic treatment, only one showed disease progression after 12 months. Notably, this patient had fHP and, despite antigen avoidance, progressed to death due to exacerbation. The choice of antifibrotic was based on a shared decision with each patient.[5] We could infer that the use of antifibrotic drugs prevented the progression of the disease in the four other siblings.

The HRCT patterns and the final diagnoses differed among the six siblings analyzed herein, corroborating the findings described in other studies.[4,7] Although UIP is the most commonly reported HRCT pattern in the literature, patterns consistent with other diagnoses have also been reported.[1,7] Most of the siblings in this series had the IPF phenotype, which has been shown to be present in 20% of patients with FIP; other studies have reported even higher rates, ranging from 54.5% to 85.9%.[1,4] In the present study, it was not possible to classify the phenotype of the sibling with an "indeterminate for UIP" HRCT pattern, perhaps because the disease was diagnosed at a very early stage. In FIP, this pattern has a prevalence of 31.4% - 55% and may be associated with the early onset of symptoms.[7]

Screening for FIP in individuals with ILD has recently taken on greater importance. One study showed that relatives of patients with FIP have a greater risk of developing ILD than the general population.[2] Results from the same study, while investigating asymptomatic relatives of patients with FIP, showed that ILA were present at the initial assessment in 22.9% of the individuals;

1. Programa de Pós-Graduação em Ciências Aplicadas à Saúde do Adulto, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brasil.
2. Departamento de Clínica Médica, Faculdade de Medicina, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte (MG), Brasil.

Table 1. Characteristics of the six siblings with familial interstitial pneumonia (FIP).

Variable	Patient					
	1	2	3	4	5 Case - index	6
Sex	Male	Male	Female	Male	Male	Male
Age (years)	81	79	75	69	65	60
Time from symptom onset to first consultation (months)	8	6	6	6	14	0
Diagnosis	IPF	IPF	fHP	IPF	IPF	Undetermined
Smoking	Yes	No	No	Yes	Yes	No
Exposure	None	None	Mold	None	None	None
GERD	Yes	No	Yes	No	Yes	No
Treatment	Pirfenidone	Nintedanib	Nintedanib	Nintedanib	Nintedanib	No
Exacerbation	Yes	No	Yes	No	No	No
HRCT pattern	UIP	Probable UIP	Consistent with other diagnoses	UIP	Probable UIP	Indeterminate for UIP
Histology	-	-	ACIF	-	IPF	-
mMRC score (at 1/12/24 months)	2/3/4	1/2/2	2/4/-	1/2/2	0/0/0	0/0/0
FVC, L (%)						
Baseline	3.27 (81%)	3.16 (81%)	1.35 (54%)	3.54 (80%)	2.99 (65%)	4.20 (94%)
12 months	3.24 (81%)	3.03 (78%)	1.13 (46%)	3.50 (75%)	2.83 (62%)	4.25 (97%)
24 months	3.06 (77%)	3.07 (78%)	-	3.41 (74%)	2.96 (65%)	4.10 (92%)
Death	No	No	Yes	No	No	No

IPF: idiopathic pulmonary fibrosis; fHP: fibrotic hypersensitivity pneumonitis; GERD: gastroesophageal reflux disease; UIP: usual interstitial pneumonia; ACIF: airway-centered interstitial fibrosis; mMRC: modified Medical Research Council (dyspnea scale); and FVC: forced vital capacity

among those, 63% exhibited disease progression within five years.[2] Exposure to tobacco and mold must be identified and ceased due to correlations with disease progression.[2] Although genetic biomarkers are known to be associated with FIP, genetic testing is currently not approved or accessible for clinical use.[4] Despite the growing scientific evidence, specific guidelines for FIP screening are not yet available. One study suggested performing HRCT in patients with respiratory symptoms or abnormal clinical examination and proposed an HRCT in asymptomatic patients at age 40 or 10 years before the age of onset in the proband; according to the authors of that study, if ILD is absent, they suggest repeating the HRCT after 5 years of follow-up.[8] In spite of the low sensitivity of PFTs, the authors also recommended these tests be conducted at the initial evaluation for all relatives of FIP patients, and, in the absence of ILD in the HRCT, the tests should be repeated within 5 years.[8] Considering this evidence, our suggestion would be to follow up first-degree relatives of patients with FIP as described above, especially those with signs of disease progression.

Data on specific antifibrotic treatments for FIP are scarce. In one study, treatment with pirfenidone reduced disease progression in patients with short telomeres.[9] Another study, although not specific for FIP, showed that nintedanib was effective in slowing the progression of non-IPF forms of ILD, such as fHP.[10] These results suggest that antifibrotic therapy may play a role in progressive fibrotic FIP, although further studies are required.

Thus, screening for ILD in relatives of individuals with FIP is necessary for the early recognition of this entity. Antifibrotic drugs may be of benefit in the management of this disease.

AUTHOR CONTRIBUTIONS

DRE, EVM, and RAC: conception and planning of the study; data collection and tabulation; statistical analysis and table creation; drafting and revision of the manuscript; formatting of the manuscript in accordance with the JBP instructions for authors, and approval of the final version.

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Brazilian Tuberculosis Research Network: 20 years of history in the fight against Tuberculosis

Ethel L. Maciel[1], Ricardo A. Arcêncio[1], José R. Lapa e Silva[1]

TO THE EDITOR,

In July 2001, a group of researchers from different fields of knowledge met in the auditorium of the Federal University of Rio de Janeiro (UFRJ) with the bold intention of creating a research network devoted to tuberculosis (TB)-related issues using a synergistic and comprehensive approach. Although the idea of launching a collaborative network was unusual at the time, since the recruited researchers often competed with each other in the past due to the scarce funding and promotion of science in Brazil, after 20 years, this decision stood out as being fundamental for the development of research on TB in the country.[1]

In 2003, the Brazilian Tuberculosis Research Network (REDE-TB) became a nonprofit, nongovernmental organization concerned not only with assisting in the development of new drugs, new vaccines, new diagnostic tests, and new strategies to control TB, but also with validating these technological innovations prior to their commercialization in the country or incorporation into the Brazilian National Tuberculosis Program.

During the past 20 years, REDE-TB has contributed to 1) the development/training of health professionals, 2) improvements in the quality of research in Brazil, with the introduction of TB as a priority theme in health policies, health agendas, and research funding, and 3) the international recognition of the network's publications, its efforts to reduce the burden of the disease by synchronism, and the establishment of essential alliances among researchers, organized civil society, managers, healthcare providers, and students, among other key actors. Because of this original, strategic, and successful approach, the World Health Organization (WHO) recognized the network as one of the most relevant achievements and recommended this strategy for other countries also affected by TB.[2]

In relation to the qualification and training of health professionals, one of the most significant successful initiatives was the development of the ICOHRTA AIDS/TB Project, funded by the National Institutes of Health (NIH), USA, a consortium involving three well-respected US Universities (Johns Hopkins, Cornell, and UC Berkeley) and the Brazilian counterparts. The project ran between 2002 and 2016 and trained over 2,000 healthcare providers in TB to conduct research in their respective workplaces.

Regarding the quality of research in Brazil, several publications have evidenced the impact of REDE-TB either in the increase in the number and impact of publications or in the networking among members, leveraging national and international collaborations.[3,4] The network has helped improve the competitivity of its members, resulting in collaborative funded projects. One example is the RePORT BRAZIL group, a consortium among members and non-members of REDE-TB, funded by the NIH and the Brazilian Ministry of Health, that was fundamental in creating and consolidating these research groups in Brazil and in helping achieve international competitivity.[5]

In addition, it is well-recognized that the scientific production of REDE-TB has contributed to boost publications in Brazil. In 2019, Migliori et al.[6] showed that Brazil was the country with the highest number of articles on tuberculosis, accounting for 208 (52.7%) of the total 395 articles from Latin America, and that the most cited authors were members of the REDE-TB group. The international renown of REDE-TB can also be noted with its participation in BRICS, where it is involved in the elaboration and operationalization of the tuberculosis research network in the countries associated with the BRICS block. Moreover, the WHO included REDE-TB in a case study for the construction of a global action framework for TB research in support of the third pillar of the WHO's end TB strategy, which was elaborated with the collaboration of its members.[2]

Furthermore, REDE-TB is an example of how the scientific collaboration model, much more than bringing people together, can be an intelligent strategy for the elimination of TB and other diseases. However, in Brazil, this is still a task for few, in the absence of funding or with unimpressive financing. It is essential that governments understand that investing in networks is the most promising way to fulfill the WHO's sustainable development goals.

AUTHOR CONTRIBUTIONS

ELM, RAA, and JRLS contributed in the conception, planning, interpretation, and writing of this letter. All authors approved the final submitted version.

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A single-center observational study on smoking behavior and preventive measures for COVID-19

Sérgio Renato da Rosa Decker[1,2], Eduardo Dambros[3], Eduardo Gehling Bertoldi[4]

TO THE EDITOR,

Studies have shown that people living with cardiovascular and respiratory diseases have poor outcomes associated with COVID-19,[1,2] both conditions being more common among smokers.[3] Liu et al.[4] analyzed factors that indicate poor prognoses in hospitalized patients with COVID-19 and found that smoking history was an independent risk factor for disease progression. Recently published comments, reviews, and observational data describe some factors that may explain the link between susceptibility to infection by SARS-CoV-2, the virus that causes COVID-19, and smoking behavior, such as upregulation of the angiotensin-converting enzyme 2 receptor and depressed immune function.[5] Therefore, it is important to analyze patterns of smoking behavior during the pandemic period, as some studies have found a bidirectional impact: people with less nicotine dependency and financial instability were more likely to attempt smoking cessation, whereas, in other groups, the smoking habit had worsened.[6] Additionally, a recent study in elderly people showed that, during the pandemic period, mask use was more common in former smokers than active smokers.[7] However, the true relationship between tobacco use and poor adherence to self-care behavior warrants further exploration.

In this sense, our study aimed to analyze the relationship between smoking status and percentual adherence to preventive measures against COVID-19 in a young population living in a middle-income country. In addition, we analyzed smoking status and adherence to preventive measures according to socioeconomic status.

A brief analysis and report, nested within a larger cross-sectional study, was conducted according to STROBE guidelines and included a sample of military personnel stationed in an army unit in Southern Brazil. Using a digital Google Form self-reported questionnaire, we collected sociodemographic data, self-reported smoking status (active smoker, former smoker, or never smoked), and information on comorbidities and adherence to preventive measures. The socioeconomic status was divided by monthly income and was categorized into < 2, 2-4, 4-10, or > 10 times the national minimum monthly wage. Active smokers also reported the number of cigarettes smoked per day and whether the pandemic period intensified their smoking behavior for descriptive purposes.

Adherence to preventive measures against COVID-19 was assessed based on six points: social isolation outside the workplace, means of transportation to work, frequency of mask use, frequency of handwashing, frequency of guests at home, and the level of agreement with the recommendations for preventing COVID-19. Most of the questions were formulated in ordinal scale format. A scoring system was developed, summarizing adherence to healthy and preventive behavior for COVID-19 into a quantitative percentage, varying from 0% (none of the questions were answered with the optimal choice) to 100% adherence to preventive measures (all six questions were answered with the optimal choice).

The ANOVA test was performed according to the Bonferroni method as a post hoc analysis when a significance level of < 0.05 (p-value) was found in the initial assessment to document the impact of smoking status on mean percentage adherence to preventive behavior. The partial eta squared was calculated to measure effect size. The same process was used to analyze socioeconomic status. Finally, when appropriate, the Chi-square or Fisher's test was conducted to measure the association between socioeconomic status and smoking status and to define whether smoking status was an independent risk factor. This study was approved by our institution's ethical committee, was carried out according to ethics standards, and all participants provided informed consent. The statistical analysis was conducted using the IBM SPSS Statistics software, Ed. 24.

A total of 475 participants were included, 9 of whom did not provide answers about smoking behavior, 2 did not answer questions related to socioeconomic status, and 7 did not answer questions regarding adherence to preventive measures against COVID-19. The data were collected in July (20.5%) and August (78.9%), 2020, concomitant to the first peak of new cases of COVID-19 in Southern Brazil;[8] the remaining 0.6% of data was collected in September. The majority of participants were male (97.7%), with low income (58.6% earned < 2 minimum wages per month), without health issues (87.4%), and never smoked (69.7%). The median percentage of adherence to preventive measures according to the devised scoring system was 50% (IQR 50% - 79.2%). Among the study participants, 46.2% had their smoking habit worsened, with a median increase of 6 cigarettes per day (IQR 5 - 10 cigarettes).

1. Programa de Pós-Graduação em Cardiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS), Brasil.
2. Hospital Nossa Senhora da Conceição, Departamento de Medicina Interna, Porto Alegre (RS), Brasil.
3. Hospital Escola de Santa Maria, Departamento de Anestesiologia, Santa Maria (RS), Brasil.
4. Faculdade de Medicina, Universidade Federal de Pelotas, Pelotas (RS), Brasil.

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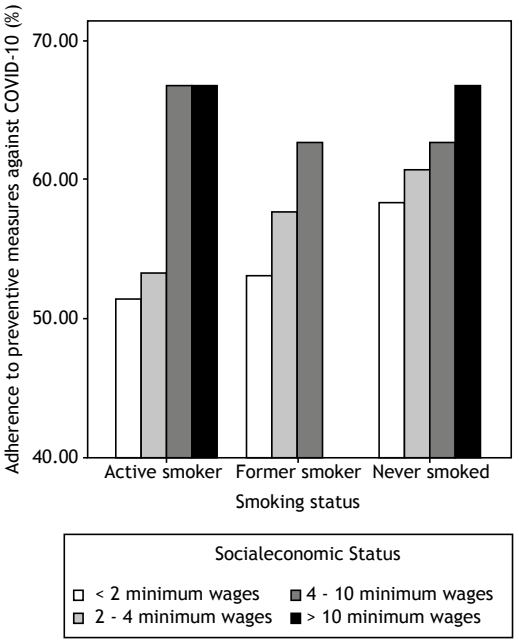

Figure 1. Mean percentage adherence to preventive measures according to smoking status and sociodemographic status.

Significant differences were found regarding adherence to preventive measures for COVID-19 according to smoking status ($F(2, 463) = 4.380$; $p = 0.013$; $\eta^2_p = 0.019$) and socioeconomic status ($F(2, 464) = 2.943$; $p = 0.033$; $\eta^2_p = 0.019$). In the Bonferroni post hoc analysis, a significant difference was observed between the active smoker status and never smokers ($p = 0.014$) and between the < 2 minimum wages group compared to the 4 to 10 minimum wages per month group ($p = 0.037$), as shown in Figure 1. We also found a significant association between smoking status and socioeconomic status ($p = 0.002$).

Our study suggests important associations of household income, smoking behavior, and the set of actions deemed essential for COVID-19 prevention. A clear dose-response relationship in adherence to preventive measures can be observed, as income rates decrease and smoking behavior increases (Figure 1). The smoking status seemed to have a greater influence on the lower-income subgroup. This finding is in agreement with another Brazilian study with an elderly population that showed a relationship in the same direction.[7] Other studies have already demonstrated that low-income populations have poorer self-care behavior and a higher frequency of smoking,[9] both of which can be important factors for more severe COVID-19 presentation.[4,10]

This study presented some limitations. The sample consisted of military personnel and included male and young subjects; thus, we must be careful about extrapolating these results to the general population. Our transversal design precludes differentiation of causation and correlation. Furthermore, our analysis, which was based on the partial eta square method, revealed a modest effect size. This may have been due to limitations inherent to our metric for preventive measures. Other ways that quantify compliance to preventive measures might show a greater difference among groups.

Finally, our study highlights an important aspect of the smoking habit: it may work as a marker for a personal tendency to undesirable behaviors in self-care, impacting on the risk of transmissible or non-transmissible diseases.

AUTHOR CONTRIBUTIONS

SRRD, ED, and EGB: study conception and design. SRRD and ED: data collection. SRRD and EGB: data analysis and interpretation. SRRD: statistical analysis. SRRD: writing of the manuscript. EGB: critical revision of the manuscript for intellectual content.

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Pneumomediastinum and pneumorrhachis as complications of dermatomyositis

Tatiana Almeida Gonçalves[1], Daniella Braz Parente[1,2], Miriam Menna Barreto[1]

A 45-year-old woman diagnosed with dermatomyositis was admitted with swelling of the neck and anterior chest wall and dysphonia for 3 days. Subcutaneous crackles were palpated on the anterior chest wall. Her hands exhibited signs of dermatomyositis (Gottron's papules, mechanic's hands, and Raynaud's phenomenon) (Figure 1A). Chest CT scan showed extensive subcutaneous emphysema dissecting the muscular planes in the neck and chest wall, pneumomediastinum, right pneumothorax, and pneumorrhachis. Interstitial lung disease was also observed (Figures 1B and 1C). Oral contrast excluded esophageal rupture. A chest CT scan performed 9 months earlier revealed a subpleural bleb in the left upper lobe and interstitial alterations (Figure 1D). The patient was treated conservatively and discharged to follow-up.

Spontaneous pneumomediastinum is an uncommon complication of dermatomyositis. Rupture of subpleural blebs or subpleural infarctions resulting from vasculitis are possible mechanisms.[1,2] In the case reported herein, the rupture of the subpleural bleb observed previously was considered the cause of the pneumomediastinum and the pneumothorax. In rare situations, air can dissect through the fascial planes from the posterior mediastinum or retropharyngeal space through the neural foramina into the epidural space, causing pneumorrhachis. This condition is usually self-limiting and conservatively managed.[3]

AUTHOR CONTRIBUTIONS

TAG: study design, data collection, and writing and revision of the manuscript. DBP and MMB: supervision of manuscript editing, writing and revision of the manuscript. TAG, DBP, and MMB: revision and approval of the final manuscript.

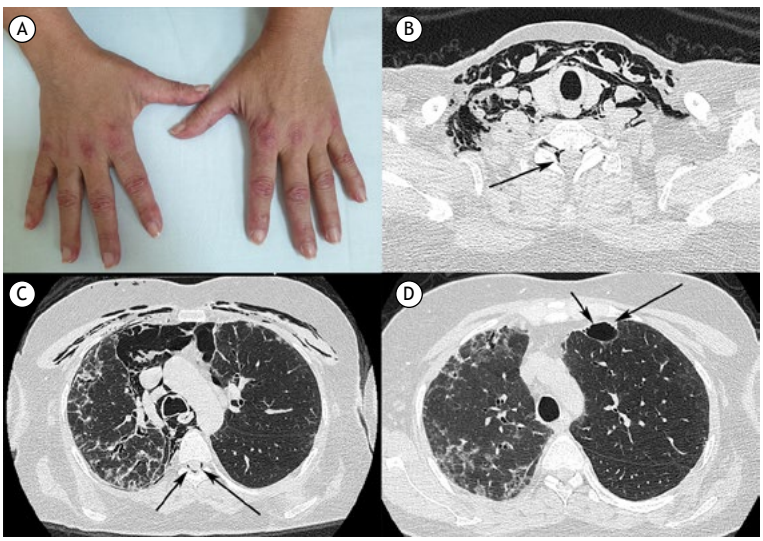

Figure 1. Forty-five-year-old woman with dermatomyositis. (A) Gottron's papules were seen on the hands due to dermatomyositis. (B, C) Axial CT images at admission showed extensive subcutaneous emphysema in the neck and chest wall, pneumomediastinum, right pneumothorax, and pneumorrhachis (black arrows). (D) Axial CT image nine months earlier showed a subpleural bleb in the left upper lobe (black arrows) and interstitial lung disease, which was more pronounced in the right lung.

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1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.
2. Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro (RJ), Brasil.

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Colon adenocarcinoma: an uncommon cause of calcified pulmonary metastases

Thiago Franchi Nunes[1], Rodrigo Augusto Melão Martinho[2], Edson Marchiori[3]

A 52-year-old man presented with chest pain, cough, and right hip pain radiating to the lower limbs for 2 months. Chest, abdominal, and pelvic CT scans demonstrated the presence of a mass with stippled calcification in the right lung (Figure 1A), a calcified mass in the liver (Figure 1B), and a lytic lesion in the right ischium (Figure 1C). PET/CT showed high fluorodeoxyglucose uptake in all lesions (Figure 1D).

The patient had a history of a moderately differentiated sigmoid adenocarcinoma, treated 6 years prior. Staging chest and abdominal CT examinations performed at the time showed no other lesions. Lung, liver, and ischial lesions were biopsied, and all corresponded to intestinal adenocarcinoma metastases. The patient was given palliative chemotherapy.

Calcifications in primary nodules suggest a benign nature, generally corresponding to granulomas or hamartomas. Several extrapulmonary primary tumors, however, are associated with calcified or ossified pulmonary metastases. These include osseous sarcomas, particularly osteosarcomas, papillary and mucinous adenocarcinomas, testicular and ovarian tumors, and medullary carcinomas of the thyroid.[1,2]

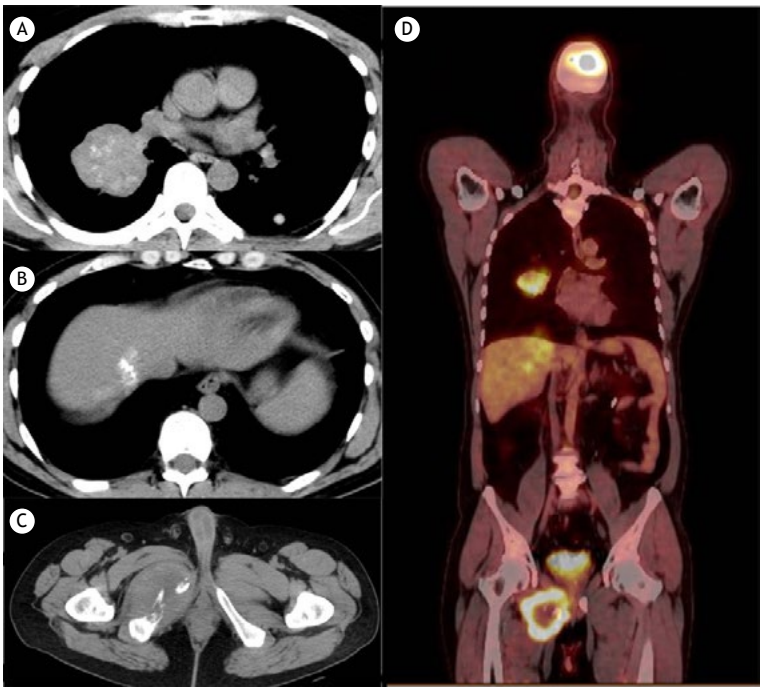

Figure 1. In A, axial chest CT image showing a mass in the right lung with stippled calcifications. Note the presence of another nodule in the left lung. Abdominal and pelvic CT demonstrated the presence of a calcified mass in the liver (B) and a lytic lesion in the right ischium (C). In D, PET/CT scan showed high fluorodeoxyglucose uptake in all lesions.

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1. Universidade Federal de Mato Grosso do Sul, Campo Grande (MS), Brasil.
2. Instituto do Câncer Brasil, Três Lagoas (MS), Brasil.
3. Universidade Federal do Rio de Janeiro. Rio de Janeiro (RJ), Brasil.

Response to "The COVID-19 pandemic and the opportunity to accelerate remote monitoring of patients"

Marco Antonio Batisti Pasquali[1], Pedro Henrique Geremias Redivo[1], Viviane Mezzomo[1], Aline Oenning Baggio[1], Chaiana Esmeraldino Mendes Marcon[1]

The editorial published in issue 4 of the *Jornal Brasileiro de Pneumologia* 2021 by Nassar Junior[1] highlighted the importance of remote monitoring of patients, which was stimulated by the COVID-19 pandemic. The author showed that telemedicine can be an ally to health services, reducing the need for face-to-face care and prioritizing the most serious cases.[1]

During the COVID-19 pandemic, there was a need to provide care remotely, as not only does this help to reduce the number of face-to-face care visits, which require, in addition to health care professionals, an infrastructure that supports both waiting rooms and patient care rooms, but also contributes to reducing the exposure of infected patients to, as well as their contact with, others who have not yet contracted the virus.[2] Systems for pre-clinical care were implemented in Brazilian cities, such as Curitiba, Florianópolis, and Recife.[2]

The remote care provided by the technical and scientific telehealth center of the state of Rio Grande do Sul, affiliated with the Federal University of Rio Grande do Sul (in Portuguese, TelessaúdeRS-UFRGS), which has been in operation for over 10 years, demonstrates the importance and highlights the benefits of this approach. By September of 2020, TelessaúdeRS-UFRGS had held more than 200,000 teleconsultations and made more than 80,000 telediagnoses. With respect to the COVID-19 pandemic, between April and July of 2020, TelessaúdeRS-UFRGS provided remote care to a specific group of patients—cases of reviews of hospital discharge after hospitalization for COVID-19—only 2.7% of whom (151 of 3,951) needed face-to-face care.[3]

Additionally, in the same way that remote care tools were applied in some cities nationwide, the Brazilian National Ministry of Health implemented the teleconsultation services of the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System), known as TeleSUS, whose system includes a smartphone application and a telephone number. Hence, this strategy served to expand the reach of health services, since approximately 17,000 calls were received between April of 2020 and April of 2021, and, of those, 5,500 were classified as high risk and callers were subsequently referred for teleconsultation with trained professionals, streamlining the service and reducing patient exposure.[4]

In addition to being used in initial patient care, telemedicine was also used to disseminate knowledge and to standardize COVID-19 patient care. An ICU telemedicine service was implemented at the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute; in this project, patient data are collected and entered into a platform specifically designed for this purpose, in compliance with the General Law on Personal Data Protection (Law no. 13,853 of 2019). Furthermore, it has web conferencing resources for case discussion. After the implementation of this service, it was found that length of ICU stay decreased by 1 day and length of hospital stay decreased by 5 days.[5]

Thinking beyond COVID-19, there are already other telehealth initiatives in operation that bring great benefits to patients, such as the one at a referral center for patients with diabetes mellitus. This diabetes-oriented telehealth service provides information to patients and caregivers so that they can treat and resolve diabetic attacks without the need to leave the house. Regarding user satisfaction, more than 80% consider the service to be good or excellent regarding the quality of guidance and care provided, usefulness, quality of health professionals, and duration of calls).[6]

It is necessary to be aware that remote health services already existed before the COVID-19 pandemic, but they have been authorized only for the duration of the pandemic. The explanation for this is that there is a legal problem, because, although the Brazilian Federal Council of Medicine has a telemedicine law, the Code of Medical Ethics prohibits prescribing drugs and procedures to a patient without a face-to-face assessment.[7]

It is evident that telemedicine is extremely useful at all stages, including screening, primary care, in-hospital care, and even post-hospital discharge care. In addition to improving protocols, telemedicine also helps reduce the burdens already known to health care systems. Therefore, in light of this, the Code of Medical Ethics must be amended to allow effective use of telemedicine beyond the borders of COVID-19, bringing gains to health professionals and especially to those who are at their most vulnerable when seeking help, that is, the patients.

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1. Faculdade de Medicina, Universidade do Sul de Santa Catarina – UNISUL – *Ringgold Standard Institution*, Tubarão (SC) Brasil.

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In the article "Consensus statement on thoracic radiology terminology in Portuguese used in Brazil and in Portugal", DOI number http://dx.doi.org/10.36416/1806-3756/e20200595, published in the Jornal Brasileiro de Pneumologia, 47(5):e20200595,2021, in the first page:

Where it reads:

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It should be read:

Marcel Koenigkam Santos

In the article "Brazilian Versions of the Physical Function ICU Test-scored and de Morton Mobility Index: translation, cross-cultural adaptation, and clinimetric properties", DOI number https://doi.org/10.36416/1806-3756/e20180366, published in the Jornal Brasileiro de Pneumologia, 46(4):e20180366,2020, in the frist page:

Where it reads:
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It should be read:
Hillana Nadiele Santos Alves

And in the odd pages header:

Where it reads:
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It should be read:
Alves HNS

ISSN 1806-3713

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3756, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

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Examples: Journal Articles

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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Chegou: EGURINEL® (pirfenidona)

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Egurinel® (pirfenidona) é bioequivalente ao medicamento referência![1]

Referência: 1. Vespasiano CFP, Accennato VAC, Costa F, Riccio MF, Bernasconi G, et al. (2020) Bioequivalence between Two Capsules of Pirfenidona in Healthy Subjects under Fed Condition. J Bioeq Stud 6(1): 101.

EGURINEL® (pirfenidona) é apresentado em embalagem contendo 270 cápsulas. **Indicações**: EGURINEL® (pirfenidona) está indicado para tratamento de fibrose pulmonar idiopática (FPI). **Posologia**: Adultos: Ao iniciar o tratamento, a dose deve ser escalonada em um período de 14 dias até a dose diária recomendada de nove cápsulas por dia, como se segue: **Dias 1 a 7**: uma cápsula, três vezes por dia (801 mg/dia). **Dias 8 a 14**: duas cápsulas, três vezes por dia (1602 mg/dia). **Dias 15 em diante**: três cápsulas, três vezes por dia (2403 mg/dia). A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. 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Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

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