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HIGHLIGHT

Consensus statement on thoracic radiology terminology

Surgical treatment of chronic thromboembolic pulmonary hypertension: the Brazilian experience

Respiratory symptoms and GOLD COPD classification system

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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Farewell, dear colleague and friend Alberto José de Araújo (August 28, 1954 – September 7, 2021)

Paulo César Rodrigues Pinto Corrêa[1,2], José Miguel Chatkin[3]

This is a huge loss and a challenging opportunity: to summarize the career of and make a tribute to an exponent of tobacco control in Brazil.

Dr. Araújo graduated from the respected *Universidade Federal do Rio de Janeiro* (UFRJ, Federal University of Rio de Janeiro) School of Medicine (1979) and specialized in Occupational Medicine at Fluminense Federal University (1995), in Social Medicine and Public Health at *Escola Nacional de Saúde Pública Sergio Arouca*, Oswaldo Cruz Foundation (1982) and in Sanitary Pulmonology at National Department of Sanitary Pulmonology at the same Foundation (1983). He was a fellow in Environmental and Occupational Medicine at the Mount Sinai School of Medicine, NY, USA (2000).[1] He earned both his Master's and Doctoral Degrees from *Instituto Alberto Luiz Coimbra de Pós-Graduação e Pesquisa de Engenharia*/UFRJ.[1] His doctoral thesis was on the cost-effectiveness of smoking cessation interventions in Brazil (2008).[1]

On February 2, 2003, the *Núcleo de Estudos e Tratamento do Tabagismo* (NETT, Center for the Study and Treatment of Smokers) was created at UFRJ.[2] The coordination of the center was initially assigned to Prof. Carlos Alberto de Barros Franco. Professionals were trained to work in the Smoking Cessation Program—an outpatient care clinic.[2] After Prof. Barros Franco's retirement in May of 2003, the program began to be coordinated by Dr. Alberto Araújo.[2] Thanks to Alberto and the NETT team's efforts, the center has gained public recognition and is today considered one of the country's reference sites in smoking cessation treatment and discussion of tobacco control policies. NETT hosts annual workshops on tobacco control strategies held by the Brazilian National Cancer Institute, the Pan American Health Organization, Johns Hopkins University, and seminars held by the Framework Convention Alliance for Tobacco Control and Campaign for Tobacco Free Kids.[2]

Honoring the tradition of pulmonologists leading tobacco control in Brazil, Alberto followed the iconic José Rosemberg's and Mário Rigatto's steps, but imprinting his own style, being extremely qualified and connected. Since 2019, he was the President of the Tobacco Control Section of the Brazilian Medical Association, being a member since 2010. He was also a member of the Licit & Illicit Drugs Committee of the Federal Council of Medicine.[1]

Dr. Alberto Araújo participated in the elaboration of the 2004 and 2008 *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) Guidelines for Smoking Cessation Treatment, and also acted as a reviewer for the 2008 Guidelines. He organized two important SBPT compilations on smoking: the 2012 SBPT Manual of Conduct and Practices in Smoking[3] and the book "Smoking: Prevention and Treatment,"[4] released earlier this year.

The name *Alberto* is of Germanic origin, derived from *Adalbert*. It originated in Portugal in the 12th century.[5] Alberto means "brilliant nobleman" or "illustrious nobleman."[5] Brilliant was Alberto indeed. A great strategist, he mastered like no one else the art of articulating and building bridges.

The meeting of one of us (PCRPC) with Alberto took place in the First Brazilian Congress on Smoking and Health, held in the city of Rio de Janeiro, in the now distant year of 2005. Reciprocal empathy and fraternal friendship germinated and hatched in a variety of ways: we participated in the World Health Organization mission to assess the Brazilian capacity for tobacco control in 2008; we cowrote *Respira Brasil*,[6] a publication we developed together at the request of the Pan American Health Organization, published at the end of 2011; and shared the management of the SBPT Tobacco Control Section in the 2011-2012 biennium.

I (JMC) have been asked when and how my encounter with Alberto happened. Before answering this question, I will bring you some considerations about "our Alberto". Sorry for my petulance in using the term "our Alberto," but as a former President of the SBPT, I dare to say it is a demonstration of affection from all Brazilian Pulmonologists.

Honestly, I do not remember a special moment of that encounter. I really believe that brothers and friends do not remember when they start to share ideas and ideals. It seems that we have always been side by side, exchanging suggestions several times a week in person, over the phone, via emails, or other media. Actually, we were looking for solutions to the countless operational difficulties regarding the smoking issue that we would have to face.

Our Alberto quickly went from being an enthusiastic contributor to initiatives related to the fight against smoking to becoming an artisan of countless achievements, introducing innovative aspects in most of his proposals.

I need to mention that Alberto and I worked with colleagues from the SBPT boards in the 2017-18, 2019-20, and 2021-22 biennia to produce a guide on smoking control containing the minimum points that all medical students should know. This proposal seemed very timely to all of us in a period when many medical schools in Brazil have no pulmonologists, but mostly internists, who are not

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always prepared for the challenge of dealing with this specific and very difficult topic. Later on, this project was expanded to the Latin American Thoracic Association, the Spanish Society of Pulmonology and Thoracic Surgery, and the Portuguese Pulmonology Society, targeting all Latin American and Iberian countries (Spain and Portugal).[7] The COVID-19 pandemic made us delay the implementation of this proposal.

So, writing about this very special person when we are still shaken by his loss was not difficult, as we all have something to say about him. We are aware of his huge list of professional qualities of the highest level and also of his affable, aggregating, and sometimes even romantic personality.

Alberto, the humanist poet, kept a website (https://ajaraujo.com.br). There he associated his texts with photos of famous canvases. A master at writing acrostics, his texts continue to be pulsating and relevant today, such as "Terra Brasilis – do golpe a la carte," written in 1996.[8]

Alberto, the political being, left us on a patriotic date: last September 7th. Perhaps it was a final act of symbolism, as he understood that the march of Brazilian democracy was unstable and went down pathways that he felt that were inappropriate.

Farewell, dear Alberto, we will all miss your presentations at SBPT events and the many good conversations in the corridors and at dinner parties.

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Getting expertise in pulmonary thromboendarterectomy: we always need to move forward!

Ricardo de Amorim Corrêa[1], Cláudio Leo Gelape[2], Rodrigo de Castro-Bernardes[3]

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the major causes of pulmonary hypertension (PH), being classified as group 4 PH by the 6th World Symposium of Pulmonary Hypertension.[1] It is one of the chronic complications of acute pulmonary embolism (PE), together with chronic thromboembolic pulmonary disease.[2] About 75% of patients with CTEPH have a documented history of PE.[1]

Chronic thromboembolic pulmonary disease and CTEPH have similar symptoms and imaging findings and differ by the presence of PH at rest in CTEPH patients. CTEPH is currently defined by the presence of a mean pulmonary arterial pressure (mPAP) > 20 mmHg with pulmonary arterial wedge pressure ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood units, at least one mismatched perfusion defect on lung scans, and findings of fibrotic thrombi on multidetector CT pulmonary angiography, magnetic resonance imaging, or conventional pulmonary cineangiography (ring-like stenoses, webs, and/or pouch or tapered lesions) after at least three months of effective anticoagulation. Pathology depicts organized thrombi and abnormal vascular remodeling due to defective angiogenesis, impaired fibrinolysis, and endothelial dysfunction.[1,2] Large and peripheral pulmonary arteries are involved, and the magnitude of the latter impacts on the clinical decision regarding the indication and the results of pulmonary endarterectomy (PEA).

The incidence of CTEPH after PE is uncertain and probably underdiagnosed, ranging from 0.4% to 8.8% (pooled incidence of 3.4%; 95% CI, 2.1-4.4%). Prevalence ranges from 0.4% to 9.1%.[3] Survival is poor, with an estimated 5-year survival of 30% when mPAP is above 40 mmHg and of 10% if it is above 50 mmHg.[4]

CTEPH is the only potentially curable cause of PH. PEA is the gold standard therapy and consists of removal of organized thrombotic lesions from the proximal vessels, that is, main, lobar, and segmental arteries (Figure 1). Refinements of the techniques and the growing expertise of surgical teams have allowed reaching more distal lesions, resulting in better short- and long-term outcomes.[5] Other options are medical therapy and percutaneous balloon pulmonary angioplasty (BPA). Riociguat is the sole drug approved for non-operable CTEPH or for patients with persistent/recurrent CTEPH after PEA.[6]

BPA has been incorporated in the arsenal for the management of CTEPH and was initially indicated for non-operable patients; however, as experience with the technique has increased in specialized centers, it has become part of a multimodal CTEPH management, together with PEA and medical therapy as complementary tools.[2,7]

A cohort study evaluated post-PEA hemodynamics and found that residual mPAP ≥ 30 mmHg correlated with initiation of pulmonary vasodilators, and residual mPAP ≥ 38 mmHg and PVR ≥ 425 dyn ··s^{-1}·· cm^{-5} correlated with poorer long-term survival.[8] Currently, the hemodynamic definition of post-PEA PH has been disputed after the new PH criteria recommended by the abovementioned symposium.[1,2]

The results of a European CTEPH Registry[9] revealed a 1-year, 2-year, and 3-year survival of 93% (95% CI, 90-95%), 91% (95% CI, 87-93%), and 89% (95% CI, 86-92%), respectively, in operated patients (n = 404/679) and of 88% (95% CI, 83-91%), 79% (95% CI, 74-83%), and 70% (95% CI, 64-76), respectively, in non-operated patients (n = 275/679), highlighting the central role of PEA. Mortality in operated and non-operated patients was associated with New York Heart Association (NYHA) class IV (hazard ratio [HR] = 4.16 [95% CI, 1.49-11.62]; p = 0.0065 vs. HR = 4.76 [95% CI, 1.76-12.88]; p = 0.0021); increased right atrial pressure (HR = 1.34 [95% CI, 0.95-1.90]; p = 0.0992 vs. HR = 1.50 [95% CI, 1.20-1.88]; p = 0.0004); and history of cancer (HR = 3.02 [95% CI, 1.36-6.69]; p = 0.0065 vs. HR = 2.15 [95% CI, 1.18-3.94]; p = 0.0129).[9]

Other authors have reported 1-month, 1-year, and 3-year survival rates of 97.2%, 93.1%, and 92.5%, respectively, after PEA.[10] They found significant improvement in NYHA class and in six-minute walk distance, as well as a reduction in PVR from 773 ± 353 dyn ··s^{-1}·· cm^{-5} to 307 ± 221 dyn ··s^{-1}·· cm^{-5} ($p < 0.001$) after the procedure.[10]

In this issue of the *Jornal Brasileiro de Pneumologia*, Scudeller et al.[11] present a retrospective analysis of their PEA results in the largest PEA referral center in South America over a 10-year period. They compared three sequential periods of time along with improvements in clinical, anesthetic, and surgical management of the patients: group 1 (January 2007-December 2012), group 2 (January 2013-March 2015) and group 3 (April 2015-May 2016). Previous PE was confirmed in 80% of the sample, and there were no differences in clinical or hemodynamic parameters among the groups, suggesting that the results might have derived from the technical improvement itself, even if we consider the retrospective design of the study. The 2-year survival probability after surgery for groups 1, 2, and 3, respectively, was 70%,

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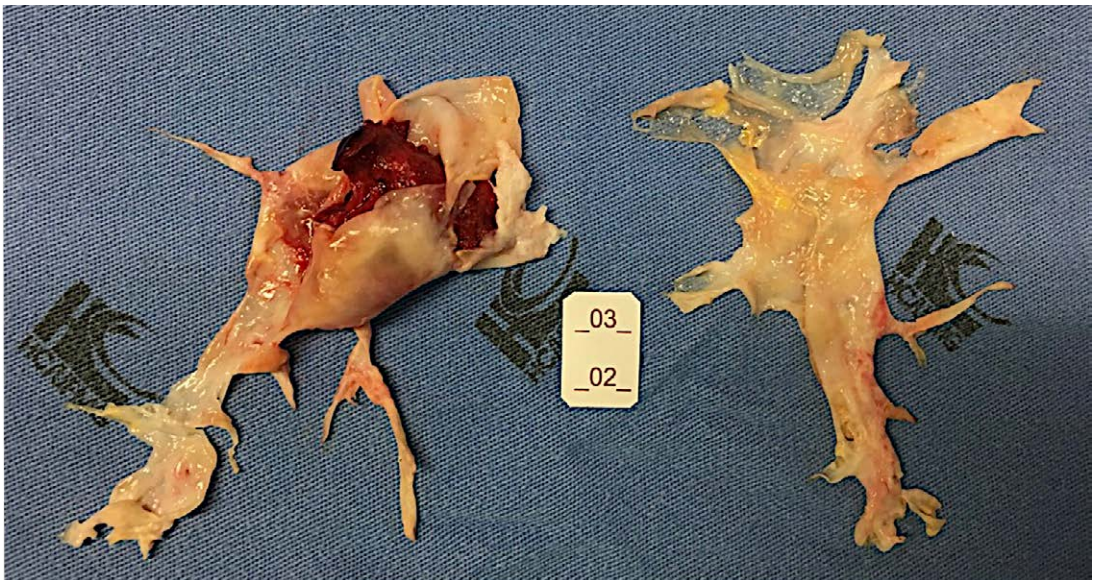

Figure 1. Bilateral pulmonary arterial thrombotic lesions removed by pulmonary thromboendarterectomy. Image kindly provided by the Clinical and Surgical Team of the *Hospital das Clínicas* of the Federal University of Minas Gerais.

77%, and 88% (p = 0.501), somewhat smaller than that reported in a previous study,[9] but there was a reduction in early post-operative complications in group 3 (10.3%) vs. groups 1 and 2 (34.2% and 31.4%, respectively; p = 0.035).

The authors examined variables potentially associated with surgical and infectious complications, as well as with in-hospital mortality. In the multivariate analysis, being in group 3 was associated with fewer surgical complications (OR = 0.221 [95% CI, 0.052-0.939]; p = 0.034 for the comparison of groups 1 and 3). In addition, high pulmonary artery systolic pressure was associated with more surgical complications (OR = 1.031 [95% CI, 1.007-1.056]; p = 0.012), and preoperative NYHA classes III-IV were associated with more infectious complications than were preoperative NYHA classes I-II (OR = 3.538 [95% CI, 1.107-11.309]; p = 0.033). Older age (OR = 1.06 [95% CI, 1.02-1.10; p = 0.047) and higher PVR (OR = 1.00 [95% CI, 1.00-1.01]; p = 0.024) were associated with higher in-hospital mortality. Mortality was 6.2 and 4.1 times more likely to occur in patients ≥ 60 years of age and in those with PVR ≥ 860 dyn ··s^{-1}·· cm^{-5}, respectively. During the follow-up period, 75.0%, 61.5%, and 63.1% of the patients in groups 1, 2, and 3, respectively, were classified as NYHA I at 3-6 months after PEA, and 58.5% of the patients who underwent right heart catheterization developed residual PH.[11] Although hemodynamic definition of residual PH was not reported, the result is higher than was that found in a large recent meta-analysis (25%).[12]

PEA is the gold standard therapy for the treatment of CTEPH, improving outcomes such as clinical and survival rates. Of utmost importance is the continuous improvement in the surgical and anesthetic techniques, as well as in the post-operative care, as has been shown by Scudeller et al.[11] Medical therapy and BPA currently play an important role in the multimodal therapy of CTEPH, which may improve the results and prognosis of these patients even further.

AUTHOR CONTRIBUTIONS

All of the authors equally contributed to the writing and reviewing of the document.

CONFLICT OF INTEREST

None declared.

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A shadow in the GOLD ABCD classification system: measurement of perception of symptoms in COPD

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"If someone separated the art of counting and measuring and weighing from all the other arts, what was left of each (of the others) would be, so to speak, insignificant."

Plato, ancient Greek philosopher

COPD is a complex disease with a heterogeneous clinical presentation,[1-3] the severity of which being related not only to functional impairment.[1] Self-reported perception of dyspnea, a subjective description of breathing discomfort, varies in intensity and derives from physiological, psychological, social, and environmental interactions[4]; a range of qualitatively different descriptors of breathing discomfort (for example, unrewarded inspiration, inspiratory difficulty, or tightness) may be however reported by COPD patients.[4] It should be noted that COPD patients with a high degree of dyspnea may also have poor maximum exercise capacity in association, regardless of the severity of airflow obstruction.[5] In addition, dyspnea is not the only symptom reported by COPD patients: respiratory health status and how COPD impacts these patients may enclose a series of clinical aspects, improving the identification of patient-reported outcomes.[1] In a nutshell, COPD may affect the patient's perception in several ways. Therefore, although COPD-related symptoms are reported as being subjective, we should find a measuring system: Plato taught us that art that is not measured is insignificant.

The modified Medical Research Council dyspnea scale (mMRC) and the COPD assessment test (CAT) have been proposed to assess symptoms quantitatively.[6] The mMRC scale is a simple clinical discriminative scale that measures the perception of dyspnea by defining the level of physical activity that provokes the symptom to appear, whereas CAT is a self-administered questionnaire that measures health-related impacts on COPD patients, exploring not only dyspnea-related aspects.[6] Both mMRC and CAT have good prognostic power, but they particularly explore daytime symptoms, although the presence of respiratory symptoms, such as nocturnal dyspnea, may have prognostic implications during the 24-hour day.[7] In order to evaluate the symptom perception of COPD patients, the GOLD 2019 report,[1] which includes the ABCD classification system, recommends using either the mMRC scale or the CAT, with no differentiation between the two. Measurements of symptoms, by using the specific cutoffs of mMRC (≥ 2 points) and CAT (score ≥ 10), define which patients have a worse perception of their symptoms; these measurements classify the risk of exacerbations into four categories.[1]

In the present issue of the Brazilian Journal of Pulmonology, the study by Montes de Oca et al.[8] reports data from a large cohort of Latin American COPD outpatients—the designated LASSYC study—and explores the value of the perception of symptoms in the context of the GOLD ABCD classification system, revealing two relevant findings. First, the patients with a worse perception of their symptoms, in accordance with the proposed cutoffs of mMRC and CAT, were distributed into different categories of risk. Second, the patients having symptoms during a 24-hour day were better identified by CAT than by the mMRC scale using the GOLD ABCD classification system. Over the years, the GOLD has shed light on several aspects of COPD, such as the importance of the disease centralizing the knowledge of specific clinical aspects of the disease. However, a subliminal question appears thanks to the study by Montes de Oca[8]: are we using suitable measurements to define different levels of COPD severity?[9] An American mathematician and computer scientist, Grace Murray Hopper, said, "One accurate measurement is worth a thousand expert opinions." When defining the patients with a higher perception of symptoms, in accordance with the GOLD ABCD classification system, there is no equivalent use of the cutoffs of the mMRC scale and the CAT score.[8] In this context, the mMRC scale and the CAT score give us information about two aspects derived from the patients' self-perception: the severity of dyspnea and the impact of the disease, although we should not forget that dyspnea is one, but not the only symptom of COPD. The GOLD classification using the CAT score is probably more sensitive to identify patients' unexplored characteristics related to the perception of symptoms during a 24-hour day.[8] Nonetheless, if these two methods of measurement are different, the GOLD groups in which we place the patients will differ, unfortunately affecting the prediction of disease progression and therapeutic revision. To characterize the disease by two different objective measures means to observe two different patients!

In the study by Montes de Oca et al.,[8] a focus needs to be placed on COPD patients perceiving more symptoms (B and D groups). In these patients, the possibility to discriminate symptoms during a 24-hour day is prevalent, and a therapeutic adjustment, according to the GOLD document,[1] needs to be made. These two groups (B

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plus D) represented 56% and 73% of the patients, respectively, using the mMRC scale and the CAT score, whereas the distribution of patients at an elevated risk of exacerbation (C plus D groups) was lower and similar (37%) regardless of the assessment tool. In a nutshell, the LASSYC study involved an excellent cohort of symptomatic COPD outpatients by evaluating the presence of symptoms during a 24-hour day. In this context, the CAT score (rather than the mMRC scale), thanks to the multidimensional assessment of the complexity of COPD, seems to be abler to identify unexplored perceptions of patients, as demonstrated by the strong correlation with the intensity of daytime symptoms.[10] Of note, the CAT score also discriminates COPD patients with small airway dysfunction.[11] However, the cutoff point of 10 for CAT cannot be used as an equivalent to the cutoff point of 2 for mMRC: there is a greater Youden index for 1 point than for 2 points on the mMRC scale. It is time to revise this aspect in the GOLD document.

A final consideration should be made. The staging of COPD patients in the GOLD document[1] starts *de facto* from the exploration of the effect of an aimed therapy (bronchodilators or inhaled corticosteroids) on a target population (COPD patients with a worse perception of symptoms or with an elevated exacerbation risk): this may define categories of patients with different needs, but it does not define the progressive levels of disease severity. Due to the complexity of COPD, an objective marker of disease progression is yet to be defined. However, the patients' ability to move (primary function, exercise, physical activity, or a muscle biological surrogate),[12] for example, might be an indirect sign of the real impact of a respiratory disease in an organism, being an important patient-derived outcome. We learned that having different results according to different measures of subjective symptoms may give us a different measure of disease.

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Mechanisms of exercise intolerance after COVID-19: new perspectives beyond physical deconditioning

Eloara Vieira Machado Ferreira[1], Rudolf K. F. Oliveira[1]

The long-COVID-19 or post-COVID-19 syndrome is defined as the persistence of symptoms after four weeks of viral infection onset, in the absence of viral replication for 3 weeks.[1] Several studies have shown that approximately 60-70% of patients report persistence of symptoms for weeks to months after acute presentation. The primary symptoms include fatigue/muscle weakness, dyspnea, depression/anxiety, and sleep and cognitive disturbances. It remains unknown why several COVID-19 patients develop chronic symptoms following the acute event. Moreover, it seems that these chronic symptoms do not correlate well with the severity of the acute clinical presentation.[2,3] The main hypotheses to explain these findings relate to the viral toxicity itself, changes in the immune system, systemic inflammatory response, endothelial and microvascular injury and/or microthrombi, fibroblast proliferation due to diffuse alveolar damage, in addition to mechanical stretch from ventilation, medications (corticosteroids, neuromuscular blockers, etc.), prolonged hospitalization with immobility, and post-traumatic stress syndrome.

Considering this scenario, it would be expected, from a pathophysiological standpoint, that those patients would demonstrate reduced exercise tolerance with decreased aerobic capacity. However, according to the literature, few studies have investigated the role of cardiopulmonary exercise testing (CPET) in COVID-19 (Table 1). Based on those studies, it has been suggested that exercise intolerance could result from physical deconditioning.[4-6] But what is physical deconditioning? In the medical dictionary, it is defined as the "loss of physical fitness due to the inability to maintain an optimal level of physical activity or training. Inactivity for any reason can lead to deconditioning." Regarding CPET findings, physical deconditioning can be described as the reduction of peak VO_2 with or without slight tachycardia in the absence of known central and peripheral cardiocirculatory diseases. The presence of an early lactate threshold, for example, is only found in individuals without central cardiocirculatory diseases who are extremely sedentary and with high muscle impairment due to inactivity, as is the case of patients with debilitating chronic diseases.

In terms of the evaluation of exercise intolerance mechanisms by CPET, it is important to define whether the effort limitation is due to a central or peripheral cardiocirculatory origin and whether there is a ventilatory or gas exchange limitation alone or associated. Exercise limitations of central cardiocirculatory origin, for example, can occur even in the presence of normal cardiac exams at rest and can be related to low O_2 delivery. Considering the hypothetical presence of myocarditis and endothelial/pulmonary microvascular lesions in the acute phase of COVID-19 infection, the exercise limitation in the post-COVID-19 syndrome related to central cardiovascular origin could be due to chronic inflammatory myocardial lesions - the prevalence of clinical and subclinical myocarditis in college athletes was 2.3% by cardiac MRI and may be one of the reasons for reduced performance in this population[7] - or pulmonary microvascular lesions. Pulmonary vascular disease, detected exclusively under physical stress, is also called exercise pulmonary hypertension'. In addition to cardiac pump impairment, the delivery of O_2 could also be compromised by reduced O_2 transport due to anemia, especially after discharge.[8]

From the peripheral standpoint, exercise intolerance may be due to impaired peripheral O_2 utilization or reduced peripheral O_2 extraction due to mitochondrial injury, with a consequent negative impact on energy production during cellular respiration for ATP formation. In keeping with this, Baratto et al.[8] demonstrated that post-COVID-19 patients at hospital discharge had a higher cardiac output (CO) at rest, lower arterial O_2 content (reduced convective O_2 transport), and a lower arteriovenous O_2 difference compared to healthy controls, but with similar O_2 extraction. During exercise, despite the higher CO, post-COVID-19 patients had lower muscle O_2 extraction in the absence of increased pulmonary artery pressure and pulmonary vascular resistance, justifying the lower peak VO_2.[8] When evaluating patients with persistent symptoms after COVID-19 infection, Singh et al.[3] elegantly demonstrated, through invasive CPET, that O_2 delivery was normal and associated with reduced peripheral O_2 extraction and elevated mixed venous O_2 saturation compared to controls, resulting in reduced peak VO_2, indicating lower diffusive O_2 delivery to the mitochondria.[3] In their study, none of the patients presented central cardiocirculatory limitations. Corroborating with peripheral muscle impairment due to mitochondrial cellular respiration dysfunction, and not to peripheral muscle deconditioning, a recent case report with muscle biopsy performed after 3 weeks of mild COVID-19 infection evidenced a reduced actin:myosin ratio with loss of myosin filaments, thus confirming the presence of primary myopathy by COVID-19 as a cause of chronic fatigue.[9] These findings open a

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new perspective that suggests that myopathy due to viral injury might be responsible for the persistence of fatigue in long-COVID-19. Similarly, it is hypothesized that these patients may develop post-viral myalgic encephalomyelitis/chronic fatigue syndrome with possible associated small-fiber neuropathy, as previously described in other viral infections, or damage to olfactory sensory neurons, causing reduced cerebrospinal fluid flow, with congestion of the glymphatic system and subsequent toxic accumulation in the central nervous system.[10,11]

Reduced peak VO_2 has not been the only finding described in post-COVID-19 syndrome. Some studies have reported mild hyperventilation due to an increase in the minute ventilation to carbon dioxide output ratio ($V'E/V'CO_2$) during exercise, which could be justified by an increase in central chemosensitivity[3] or by dysfunctional breathing,[5,6] which would reduce the arterial CO_2 pressure by increasing the ventilatory drive. It is noteworthy, however, that systemic stimuli of ventilation, such as activation of metabo- and mechanoreceptors during exercise, present in the peripheral muscles, can also justify the increase in $V'E/V'CO_2$ in the absence of pulmonary and cardiac sequelae.[3] Another possible cause for ventilatory inefficiency would be the increase in dead space as a fraction of tidal volume (VD/VT), which may be present in patients with endothelial and/or microvascular injury, poor alveoli perfusion, and/or destruction of the pulmonary vascular bed in fibrotic areas, associated with reduced O_2 diffusion through the blood-alveolar barrier.[3,8] This hypothesis would be plausible to justify, for example, the hypothetical presence of exercise pulmonary hypertension (not confirmed so far in the literature).[3,8] The VD/VT could also be elevated as a consequence of the reduction in VT during exercise due to the persistence of interstitial pulmonary fibrosis with consequent changes in ventilatory mechanics and ventilatory limitation, with possible associations with the extent of acute interstitial pulmonary involvement.[12] Finally, the presence of effort-induced hypoxemia could reduce muscle O_2 delivery, causing limitations in gas exchange.[5]

Thus, considering the current pathophysiological knowledge of intolerance mechanisms and the range of systemic manifestations of the acute phase of COVID-19 infection, it would be simplistic for us to consider that all chronic symptoms of the long-COVID-19 syndrome

Table 1. Summary of the main studies evaluating exercise intolerance in patients after COVID-19 infection.

Time of evaluation sample (n)	Dyspnea (mMRC)	Subgroups	Peak VO_2 in the sample	Findings
Rinaldo et al.[2] 3 months (n = 75)	57%	Severity of hospitalization: mild-moderate, severe, and critical	54% (VO_2 < 85%prev) (*post hoc* analysis)	Older Greater residual pulmonary sequelae No difference in lung function No difference in peak VO_2 in cardiocirculatory and gas exchange responses. Mild increase of $V'E/V'CO_2$ in the critical *vs.* mild-moderate group
Rinaldo et al.[4] 3 months (n = 75)	52%	Reduced or normal peak VO_2	55% (VO_2 < 85%prev)	Lower lactate threshold Lower $\Delta VO_2/\Delta WR$ Lower pulse O_2
Skjørten et al.[5] 3 months (n=156) (multicenter)	47%	Comparison with normal population without COVID-19 by z-score (20% in ICU)	89 ± 17%prev 31% (VO_2 < 80%prev)	15% reduced lactate threshold 16% ventilatory limitation 23% desaturation >4% 15% increased $\Delta V'E/\Delta V'CO_2$
Motiejunaite et al.[6] 3 months (n = 114)	Dyspnea 40% Fatigue 32%	DCO ≤ or > 75%prev	75% (VO_2 < 85%prev)	Smallest peak VO_2 Lower lactate threshold Tendency to greater limitation to exercise
Liu et al.[12] 7 months (n = 41)	-	Persistence or absence of pulmonary fibrosis on chest CT	16.4 ± 3.6 mL/kg/min (with fibrosis) 20.2 ± 3.7 mL/kg/min (no fibrosis)	Older and more severe hospitalization Smallest peak VO_2 Lower METS Higher $V'E/V'CO_2$
Debeaumont et al.* 6 months (n = 23)	78%	ICU *vs.* ward	52% (VO_2 < 85%prev)	Higher $\Delta V'E/\Delta V'CO_2$
Dorelli et al.** 5 months (n = 28)	-	$\Delta V'E/\Delta V'CO_2$ > 31 or ≤ 31	29.2 ± 8.3 mL/kg/min	No difference in pulmonary function variables at rest and in CPET responses

Abbreviations: mMRC: Medical Research Council modified dyspnea scale; peak VO_2: peak exercise oxygen consumption; WR: work rate; $V'E/V'CO_2$: minute ventilation by carbon dioxide output; DCO: carbon monoxide diffusion; chest CT: chest computed tomography; ICU: intensive care unit. *DOI:https://www.doi.org/10.1093/ptj/pzab099 **DOI: https://www.doi.org/10.3390/diagnostics11030507.

are due to physical deconditioning by inactivity or prolonged hospitalization. The physical deconditioning theory does not explain the presence of persistent symptoms in patients who were affected by mild forms of the disease, many of whom did not even require hospitalization. Similarly, this theory does not explain the dissociation between the severity of hospitalization and the reduction in peak VO_2 reported so far, nor does it explain the antagonism of the persistence of symptoms in patients with preserved peak VO_2.[4-6]

In light of the potential complexity and the lack of knowledge on the post-COVID-19 syndrome, it is unacceptable to be simplistic when attempting to unravel the post-COVID-19 syndrome exercise intolerance mechanisms. More robust scientific evidence is needed before drawing simple conclusions.

AUTHOR CONTRIBUTIONS

EVMF and RKFO: preparation, writing, and revision of the manuscript.

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The reversed halo sign in COVID-19

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

Two patients diagnosed with COVID-19, confirmed by RT-PCR, presented distinct aspects of the reversed halo sign on chest computed tomography (CT) scans (Figure 1).

The reversed halo sign (RHS), seen on chest CT scans, is defined as a rounded or oval area of ground-glass opacity, completely or partially surrounded by a consolidation ring. This sign is described not only in organizing pneumonia (OP) but in a broad spectrum of infectious and non-infectious diseases. Despite being considered a nonspecific sign, the careful analysis of its morphological characteristics can narrow down the differential diagnosis, helping assistant physicians establish the definitive diagnosis.

The RHS in patients with COVID-19 may be related to associated infectious diseases, or might be due to the evolutionary phases of COVID-19 itself. The primary alterations related to COVID-19 that can occur with RHS are OP and pulmonary infarction. This differential diagnosis is extremely important, as different therapeutic approaches will be needed. RHS secondary to the organization of the inflammatory process, with OP, presents with the classical aspect of ground-glass opacities surrounded by a halo of consolidation.

Areas of low attenuation within the halo, with or without reticulation (reticular RHS), strongly suggest pulmonary infarction. The subpleural and inferior pulmonary location, as well as the occurrence of pleural effusion in association with RHS, may also favor this diagnosis. In reticular RHS, the patient's immunological status is the most important clinical information for the differential diagnosis. In immunodeficient patients, the main diagnostic hypothesis is invasive fungal diseases. Meanwhile, in immunocompetent patients, the finding of reticular RHS, in general, corresponds to pulmonary infarction. The pathophysiology of vascular disease in patients with COVID-19 is controversial and may involve *in situ* microvascular thrombosis or pulmonary embolism originating from pelvic or lower limb veins. Since pulmonary vascular disease in COVID-19 mainly

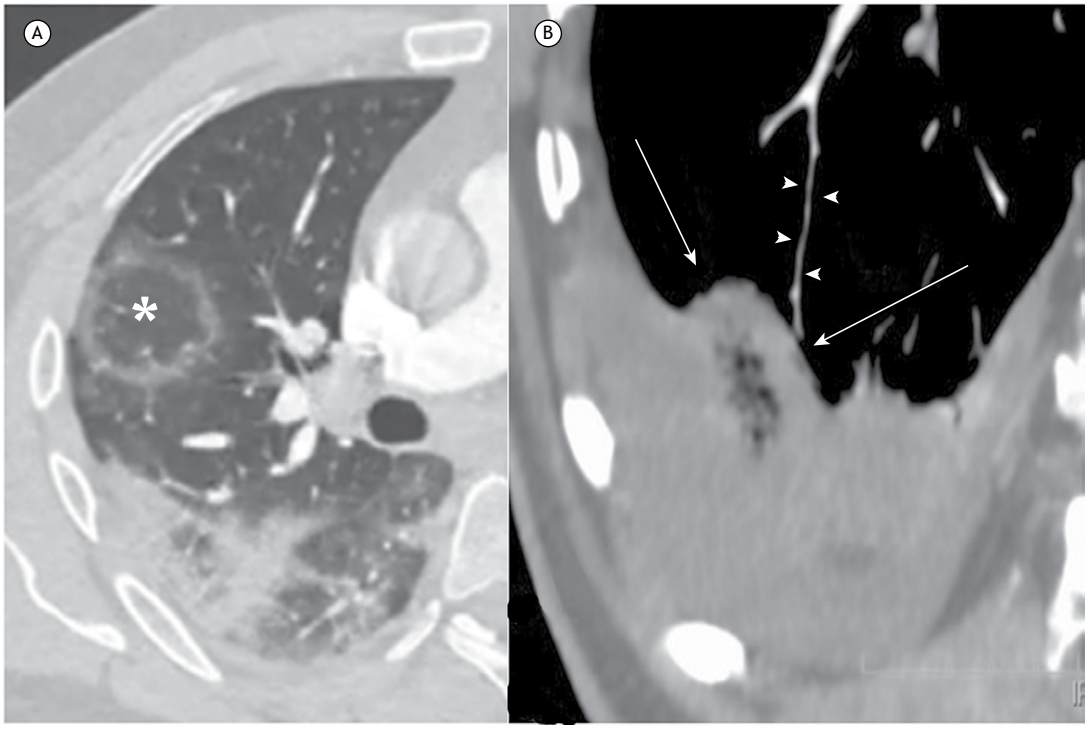

Figure 1. In A, classical reversed halo sign, with rounded ground-glass opacity surrounded by a halo of consolidation (asterisk). Also note the consolidation in the posterior lung parenchyma. In B, reticular reversed halo sign (arrows) with an aspect of central reticulation and peripheral, subpleural location, in addition to associated pleural effusion. Note also the thinning of the adjacent artery, with an aspect of irregularities in its contours (arrowheads).

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involves segmental and subsegmental arteries, some authors suggest that the development of pulmonary infarction in COVID-19 is more often attributable to pulmonary vessel thrombosis caused by severe pulmonary inflammation and hypercoagulability than to thromboembolism[1,2].

In conclusion, the RHS is a common, non-contrast CT finding in patients with COVID-19 that may be related to two distinct pathophysiological events with different imaging characteristics: classical RHS, suggestive of diagnosis of OP, and reticular RHS, which suggests the diagnosis of pulmonary infarction, especially when accompanied by pleural effusion, sudden clinical worsening, and elevation of the D-dimer. Under these conditions, unless contraindicated, CT pulmonary angiography should be considered.

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Implementation research and its role in public health and health policies

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PRACTICAL SCENARIO

A ministry of health, worried about the increase in the prevalence of current smoking among their adult population, surveyed a sample of this population to identify barriers to smoking cessation. The results showed that current smoking cessation interventions, based on visiting a pulmonologist, were not feasible because of important barriers, including difficulties in scheduling an appointment and adhering to follow-up visits, leading to loss of motivation. These results were used to inform the development of a population-based smoking cessation intervention through a mobile app to evaluate its feasibility and effectiveness.

IMPLEMENTATION RESEARCH

Implementation research (IR) is a specific scientific approach that evaluates the effectiveness of incorporating evidence-based interventions and policies into the routine health care system. IR focuses on facilitators of and barriers to implementing evidence-based interventions in public and private health care systems and promotes the application, use, and sustainability of these interventions on a large scale (Figure 1).

IR evaluates different types of interventions, including newly developed medical devices and technologies, application of treatment protocols, service delivery programs, behavioral interventions, among others. Social science research methods, as well as methods for determining the cost of implementation strategies at different levels of the health care system[1] are used in IR.

HOW CAN IR IMPROVE PUBLIC HEALTH?

IR addresses health policy makers' priorities and the needs of real-world health decision makers. Although successful efforts have been made to close the research gap in changing health policies, health decision-making processes are highly complex and involve a great number of stakeholders. Conducting policy-driven research, such as IR, supports the use of research findings to inform health policy planning and its implementation by policy makers.[2]. Thus, the main role of IR is to improve the effectiveness of health care systems and health care delivery.

CONSIDERATIONS WHEN CONDUCTING IR

***Population*:** IR is ideally conducted within the population that will be affected by the health-related intervention. The selection of inclusion criteria should be broad and result in a study population that is truly representative of the target population, whereas exclusion criteria should be minimal. In our example, the population consisted of adult smokers from all regions of the country who have access to a smartphone.

***Intervention/Exposure*:** interventions that fall under IR are broad. They may be complex, and the research team should try to involve diverse stakeholders. In our example, the intervention was the use of an app to promote behavioral interventions for smoking cessation. Stakeholders included the ministry of health, the general population, health professionals working in smoke cessation programs, etc.

***Comparator*:** the analytical approach of IR differs from the approach used in clinical research. Usually, the intervention has already been shown to be effective within the controlled environment of a clinical trial. In IR, the objective is to test the application of an intervention in real-world settings and if it continues to be effective over time. Therefore, a comparison group may not be necessary, or historical controls may be used.

***Outcome*:** the outcomes are usually focused on feasibility, acceptance, adherence, and effectiveness in real-world scenarios where the intervention will be

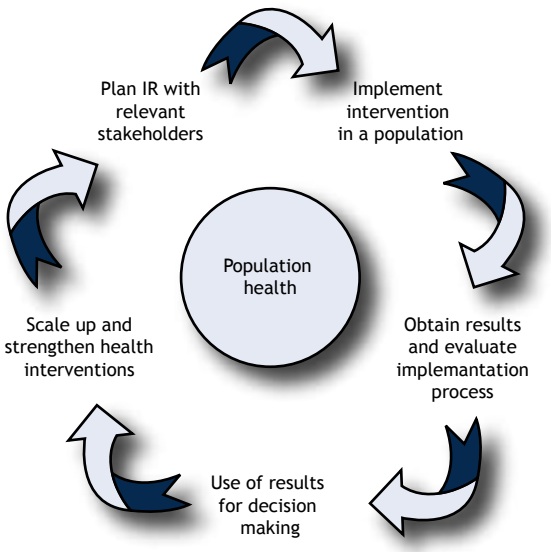

Figure 1. The process of implementation research.

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implemented. In our example, outcomes include perceived usefulness and number of interactions with the app and, most importantly, smoking cessation rates among users. IR can evaluate various outcomes simultaneously, and the results should potentially be used for decision-making processes.

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Measurements of respiratory muscle function as diagnostic criteria for diaphragmatic paralysis

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BACKGROUND

Diaphragmatic dysfunction is an underdiagnosed cause of dyspnea. Patients with unilateral diaphragmatic paralysis can be asymptomatic or present with dyspnea on exertion, which is often an incidental finding. Measurements of respiratory muscle function can aid in establishing a diagnosis and quantifying diaphragmatic dysfunction.[1,2]

OVERVIEW

A 52-year-old female patient in the late postoperative period of mitral valve replacement was referred for assessment of respiratory muscle function because of exertional dyspnea (Medical Research Council scale score = 2) and elevated right hemidiaphragm on chest X-ray.

Pulmonary function tests showed moderately reduced FEV_1 (46% predicted) and FVC (51% predicted), with normal FEV_1/FVC (88%) and reduced TLC (72% predicted). Respiratory muscle strength measurements confirmed inspiratory weakness, with low values for MIP (67% predicted), transdiaphragmatic pressure during a sniff maneuver (30% predicted), and twitch transdiaphragmatic pressure during bilateral magnetic phrenic nerve stimulation (40% predicted). Additionally, the gastric pressure (Pga) during the sniff maneuver was negative, positive values being expected during inhalation. This resulted in extremely low transdiaphragmatic pressure, reflecting diaphragmatic weakness.

Diaphragmatic ultrasound showed reduced mobility and thickness of the right hemidiaphragm during deep breathing, as well as paradoxical motion during sniffing (Figure 1A). This was probably related to the negative Pga during sniffing, with the diaphragm being sucked up into the chest, thus impairing diaphragm mechanics and respiratory pressure generation.[3]

Diaphragmatic function was also assessed by electrical impedance tomography, which showed diminished ventilation distribution in the lung corresponding to the paralyzed hemidiaphragm (approximately 29%; Figure 1B).

Cardiopulmonary exercise testing evidenced the role of diaphragmatic weakness in exercise limitation, with diaphragmatic dysfunction being evidenced by a decrease in Pga as the work rate increased. Diaphragmatic dysfunction was related to an increased RR and dyspnea for a given work rate in comparison with a healthy control (Figure 2). Studies have described patients with unilateral diaphragmatic paralysis and reduced diaphragmatic strength related to low Pga.[4,5]

CLINICAL MESSAGE

Diaphragmatic paralysis, as in the case reported here, should be considered as a cause of dyspnea. Assessment of respiratory muscle function and cardiopulmonary exercise testing can aid in establishing a diagnosis.

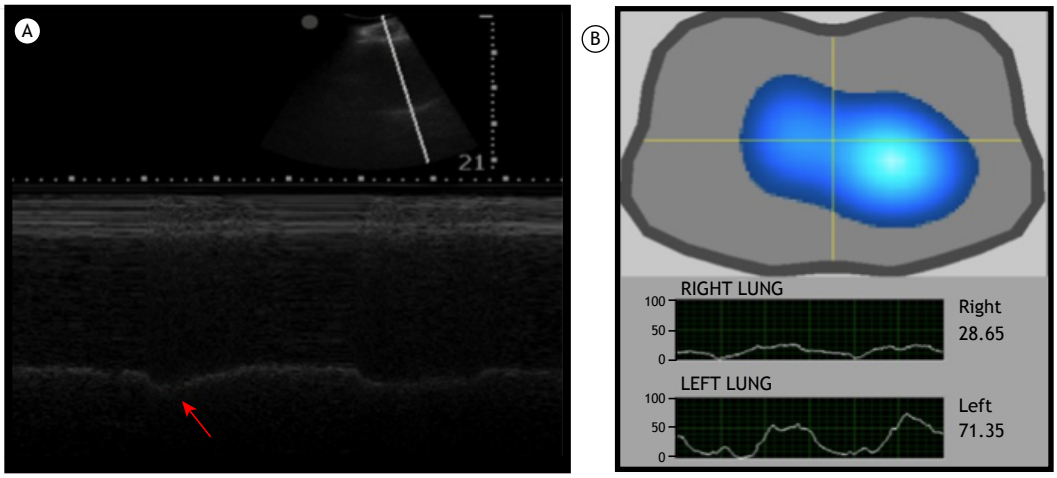

Figure 1. In A, paralyzed hemidiaphragm showing paradoxical motion during a sniff maneuver (red arrow). In B, electrical impedance tomography showing diminished ventilation distribution in the lung corresponding to the paralyzed hemidiaphragm.

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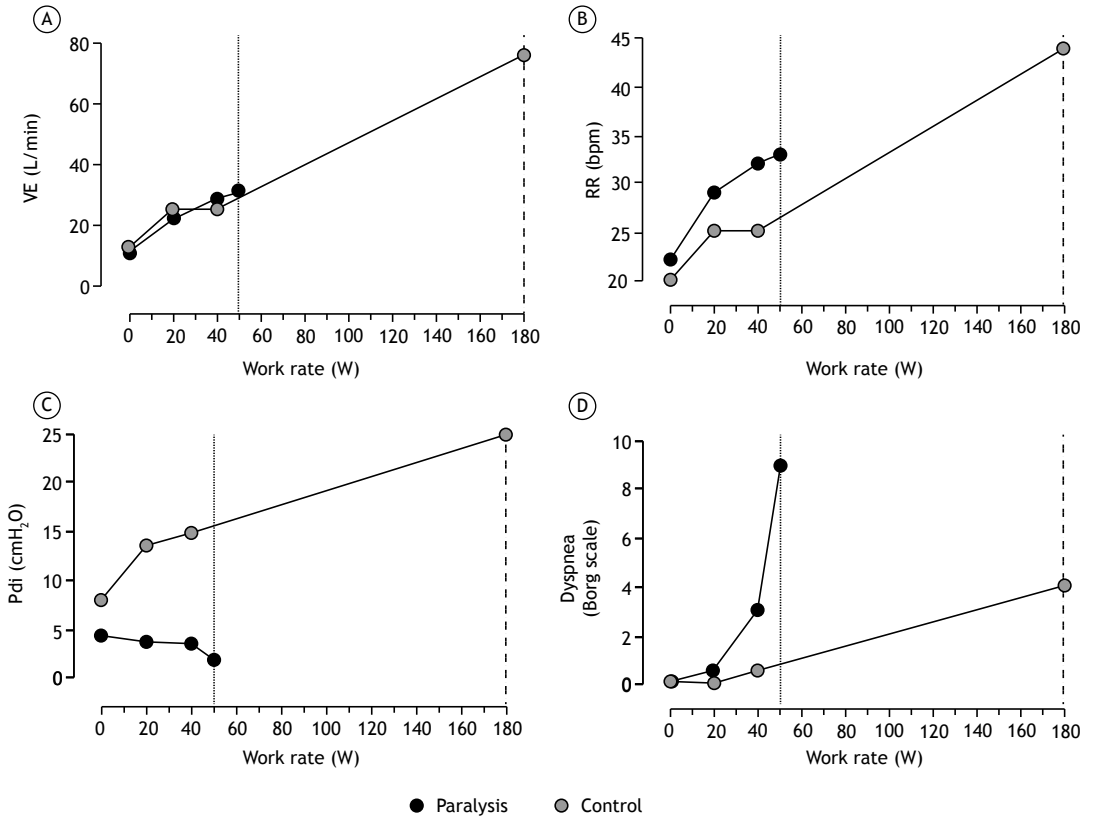

Figure 2. Cardiopulmonary exercise testing showing A) V_E, B) RR, C) transdiaphragmatic pressure (Pdi), and D) Borg dyspnea scale scores for a given work rate in comparison with a healthy control. The dotted lines represent peak exercise.

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ORIGINAL ARTICLE

Respiratory burden in obese and young asthmatics: a study of diaphragmatic kinetics

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Study carried out in the Universidade Federal de Pernambuco, Recife (PE), Brasil.

ABSTRACT

Objective: The aim of this study was to assess the diaphragm kinetics, respiratory function, and serum dosage of leptin and inflammatory cytokines (IL-6 and TNF-α) in three clinical groups: obese, asthmatic, and healthy. **Methods:** This is a clinical exploratory study performed on 73 youths (12-24 years of age, 42.5% male) allocated into three groups: obesity (OG, n=33), body mass index (BMIz-score) ≥ +2, asthmatic (AG, n=26) controlled mild asthmatics, classified by GINA, and Healthy Control Group (CG, n=14). The participants were subjected to diaphragmatic ultrasound, spirometry, maximal respiratory pressure, serum leptin levels, and IL-6 and TNF-α whole blood cell culture levels. **Results:** Diaphragm thickness was higher in OG in comparison to AG and CG (2.0±0.4 vs 1.7±0.5 and 1.6±0.2, both with $p<0.05$). Maximal voluntary ventilation (MVV) was significantly lower in OG and AG in relation to the CG (82.8±21.4 and 72.5±21.2 vs 102.8±27.3, both with $p<0.05$). OG has the highest leptin rate among the groups (with the other two groups had $p<0.05$). All groups had similar TNF-α and IL-6 levels. **Conclusion:** The muscular hypertrophy found in the diaphragm of the obese individuals can be justified by the increase in respiratory work imposed by the chronic condition of the disease. Such increase in thickness did not occur in controlled mild asthmatics. The IL-6 and TNF-α markers detected no evidence of muscle inflammation, even though leptin was expected to be altered in obese individuals. Both obese and asthmatic patients had lower pulmonary resistance than the healthy ones.

Keywords: Obesity; Asthma; Diaphragm excursion; Diaphragm thickness; Adipokines.

INTRODUCTION

Over the past decade, it has been reported that childhood obesity and asthma can lead to immunometabolic mechanisms that cause negative impact on the respiratory system.[1] Although it is well-known that obesity and asthma may alter chest mechanics, reduce lung volumes and capacities and increase airway resistance, changes in the diaphragmatic excursion and thickness in this specific population are yet to be studied[2,3] Adipokines (serum leptin, IL-6) and other inflammatory cytokines can modify the function of the diaphragm in obseve individuals throughout life.[4-7]

Ultrasound assessment of diaphragmatic kinetics can contribute to the early identification of structural changes induced by higher respiratory demand experienced by obese individuals throughout life, as well as in inter-crisis periods of asthmatics.[8,9] Our hypothesis is that obese or asthmatic youngsters may have their diaphragms impaired and adipokines altered, leading to negative impact on pulmonary function and respiratory muscle strength or resistance. This study aimed to assess the diaphragm kinetics, respiratory function, and serum dosage of leptin and inflammatory cytokines in blood cell culture (IL-6 and TNF-α) in the following three clinical groups: obese, asthmatic, and healthy young individuals.

METHODS

This is a clinical-exploratory study performed in the Pulmonary Function Laboratory of the Pulmonology Service at the Federal University of Pernambuco (UFPE)

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Clinical Hospital, in Recife, Pernambuco. Clinical Trial Registration: (Obesity-asthma Endophenotype and Diaphragm Mobility in Adolescence, NCT03029936).[10] All the participants and their guardians were informed on the research procedures and signed terms of free informed consent.

The study includes seventy-three youngsters, both male and female, aged between 12 and 24 years, allocated into three groups: Obesity Group (OG), Asthmatic Group (AG), and Comparative Group (CG). The obesity group includes thirty-three individuals diagnosed with obesity (body mass index – BMIz-score ≥+2).[11] The asthma group consists of twenty-six individuals diagnosed with persistent mild controlled asthma, according to the criteria of GINA,[12] with a BMIz-score<+2. Finally, the Comparative Group comprises 14 individuals without any respiratory or neurological diseases. Figure 1 shows the study design flowchart.

Considering the spontaneous demand of the service, we selected all patients at the hospital pediatric outpatient clinics, due to. The healthy group was composed of the healthy family members of the patients and the staff. The following exclusion criteria were applied: individuals with congenital, neurological, or genetic diseases and patients who could not respond to the procedure commands.

Initially, we assessed the anthropometric and clinical data of all participant patients. All measurements were collected from the outpatient clinic in the morning by observing a four-hour fasting at least (to assess adipokine levels). Subsequently, a diaphragmatic ultrasound was performed to assess excursion and thickness, spirometry, and maximal respiratory pressures.

Body weight and height were measured using a digital scale with 0.01 kg precision (Digital scale, Indústrias Fillizola S.A, São Paulo, São Paulo, Brazil) and a 2-m portable 0.1-cm graduation stadiometer (Stadiometer, Sanny®, São Bernardo do Campo, São Paulo, Brazil), respectively. The body mass index (BMI) calculation followed the World Health Organization (WHO) AnthroPlus program (AnthroPlus, WHO, Geneva, Switzerland) and categorized according to the BMI z-score.[11]

We assessed the body composition by measuring the seven skin folds (subscapular, middle axillary, triceps brachii, thigh, suprailiac, abdomen, and chest) using a digital plicometer (Digital plicometer DGI, Prime Med, Curitiba, Paraná, Brazil). Three measurements were performed anf followed by the calculation of the arithmetic mean among them.[13]

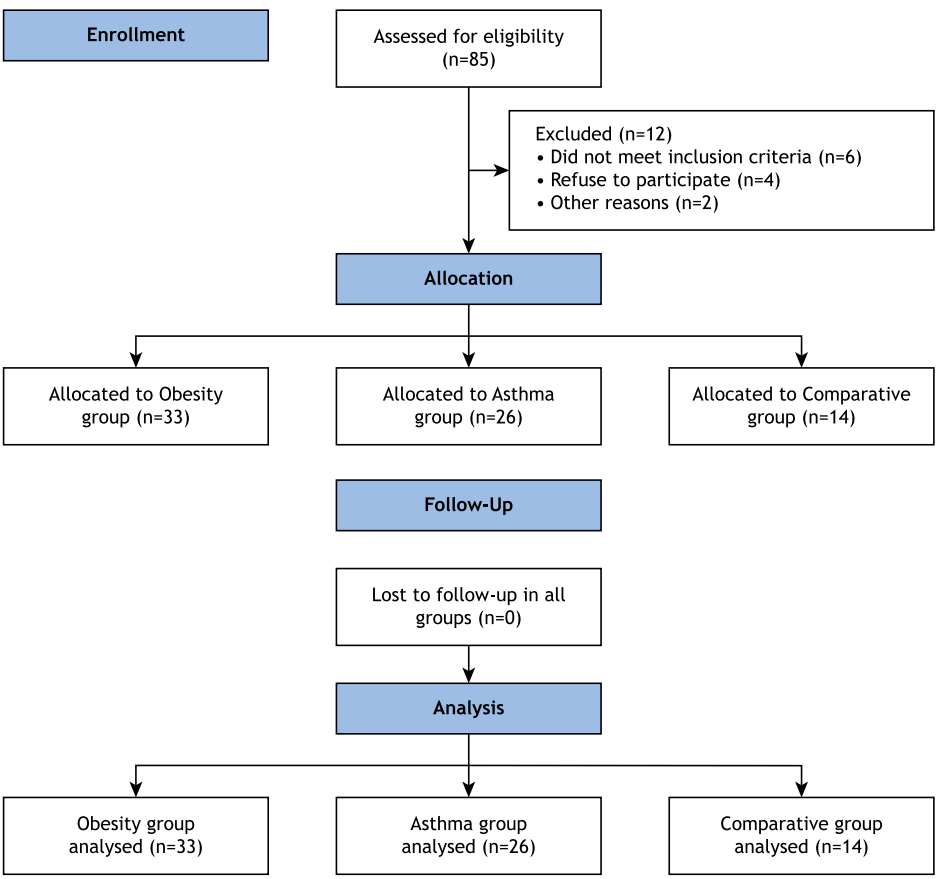

Figure 1. Study design flowchart.

We measured the diaphragmatic excursion with the individuals lying with their thorax supported on a 45° slope by performing an ultrasound (Sono Ace R3 ultrasound system, Samsung Company, Seoul, South Korea) in M mode with a convex transducer (3.5MHz), positioned at the right mid-axillary line.[14,15] Participants were instructed to breathe deeply and rapidly at the level of total lung capacity (TLC), which was repeated several times. The record of cranio-caudal diaphragmatic excursions during resting breathing and respiration until total lung capacity showed sinusoidal curves.[14,15] The diaphragmatic excursion (Dexc) appeared in the trajectory obtained between the baseline before the inspiration onset and the plateau in the total lung capacity end. We obtained the average of five measurements with a difference below 10% between them.

We assessed the diaphragmatic thickness through an ultrasound (Sono Ace R3 ultrasound system, Samsung Company, Seoul, South Korea) in B mode. The participant was positioned in the left lateral decubitus position[9,14,15] and a high-resolution, low-penetration linear transducer (7.5 MHz) was placed perpendicularly to the thoracic cavity between the eighth and ninth intercostal space between the axillary lines.[16] The diaphragm was identified by two parallel bright lines that depict the pleural and peritoneal membrane. The diaphragmatic thickness was measured from the middle of the pleural line to the middle of the peritoneal line. Two thickness measurements were performed between 0.5 and 2 centimeters of the costophrenic sinus visualization in each ultrasound image, and the mean value of these two measurements was used as the final measurement.[15] The mean of three final thickness measurements of the diaphragmatic apposition zone was obtained during the functional residual capacity (relaxed diaphragm thickness - Tfrc) and in the end of the total lung capacity (contracted diaphragm thickness – Ttlc). We also calculated the thickening fraction (TF) as the proportional thickening of the diaphragm from functional residual capacity (FRC) to total lung capacity (TLC). TF represents an index of diaphragmatic thickening as defined by the following Equation 1:

$$TF = \left[\left(Ttlc - Tfrc\right] / Tfrc\right)] \times 100 \quad (1)$$

where Tfrc is the diaphragm thickness measured in the end of a quiet expiration (at FRC), and Ttlc is the maximum diaphragm thickness measured in the end of a deep breath (at TLC).

We used a multifunctional portable spirometer (Spirobank G USB - MIR; Rome, Italy) to perform the spirometry according to the recommended standards.[17] To assess the maximum voluntary ventilation (MVV), we asked the patient to breathe as fast and deep as possible for 12 to 15 seconds. The volume mobilized in this time period was then extrapolated to the time of 1 minute. All equations used for the calculations were estimated by Pereira et al.[18]

We assessed the inspiratory and expiratory muscle strength indirectly by measuring the maximal inspiratory and expiratory pressures (MIP and MEP, respectively) using a digital manovacuometer (MVD-300, GlobalMed, Rio Grande do Sul, Brazil). To obtain the MIP, the patient was required to perform an expiration until residual volume, followed by a maximal inspiration with the airway occluded by a nasal clip. For the MEP, the patient was asked to inhale until total lung capacity, followed by a forced expiration. We performed three maneuvers with the patient sitting and considered the highest value for assessment, based on normal values for the maximal respiratory pressures in young individuals.[19]

Ten milliliters of blood were collected in tubes containing sodium heparin for cell culture. Leptin analysis was performed according to the manufacturer's recommendations using the Human Leptin Elisa commercial kit (Leptin ELISA Kit, Millipore Corporation, St Charles, Missouri, USA). Serum sample cytokine levels were quantified through the Cytometric Bead Array (CBA) system, following the methodology suggested by the manufacturer. Firstly, we transferred 50 µl of the capture beads mixture labeled with monoclonal antibodies (anti-IL-2, anti-IL-4, anti-IL-6, anti-IL-10, anti-IFNγ, and anti-TNF-α) with different fluorescence intensities (FL3) to tubes to test the samples and the negative control. Data were acquired using the FACScalibur flow cytometer and analyses were performed on the BD CBA software (BD CBA, Becton, Dickinson and Company, San Jose, USA).

Peripheral blood cells were cultured for a second day standardization performed by Lorena et al.[20] We stimulated cultures of *Dermatophagoides pteronyssinus* (DPT), *Phytohemagglutinin* (PHA) (5 µg/mL) and used cultures without stimulus as negative control. Blood was cultured in culture-specific tubes at a ratio of 1mL whole blood to 1mL RPMI 1640 medium supplemented with 10% Fetal Bovine Serum at 37°C at 5% CO_2.

We conducted the statistical testson a statistical software (SPSS, 20.0, Chigado, IL, USA) and built the figures on GraphPad Instat (GraphPad Software, San Diego, CA, USA). A Shapiro-Wilk test verified the assumption of normality and homogeneity of the quantitative variables involved in the study. One-way ANOVA with Tukey's multiple comparison test compared the quantitative and normal variables among the three groups. In case of non-normal quantitative variables, a Kruskall-Wallis test with Dunn's Multiple Comparison was applied. All correlations used Spearman coefficient. Numerical variables were presented as central tendency and dispersion measures. All conclusions resulted from a significance level of 5%.

We calculated the sample on the G*power-3.1.9.4 program through post-hoc power based on the diaphragm thickness data from three analyzed groups. The values considered were α=0.05, total sample size=73, number of groups in the one-way ANOVA test=3, and effect size f=0.4260637. The effect size was calculated based on the mean, sample size, and

square root of the combined variance for the three analyzed groups. These data generated a Power (1-β err prob) of 90%.

RESULTS

Of the total of 73 participating individuals (42.5% men), 14 (42.8% men) were allocated in the health control group (CG), 33 (39.4% men) referred to those with obesity without asthma (OG), and 26 (46.1% men) had persistent mild controlled asthma (AG).

As expected, no difference among the groups was found for either age or height, while the obesity group had higher levels of total weight, BMI z-score, lean body mass, fat mass, fat percentage, and abdominal circumference than both the asthma and comparative groups (Table 1).

Diaphragm Excursion, Thickness, and Thickening Fraction

Figure 2 shows the comparisons of diaphragmatic excursion and thickness among the groups. Regarding diaphragm kinetics, the obesity group had higher thickness at FRC than both the asthma and healthy groups. No difference was indicated between the median (interquartile range) and thickening fraction among obese, asthmatic, and healthy individuals [158 (79.5) vs 157.5 (133) vs 161 (109.9), p>0.05 - Nonparametric data-Kruskall-Wallis test]. In addition, the thickening fractions were positively correlated with fat mass and body fat percentage (r=0.431, p=0.012 and r=0.425, p=0.014, respectively)

Pulmonary Function Test and Maximal Respiratory Pressures

All three study groups had spirometric variables, including forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), within the normal range (table 2). Both the obese and asthma groups had significantly lower mean MVV% than the healthy individuals (Table 2). All groups had similar maximal respiratory pressures.

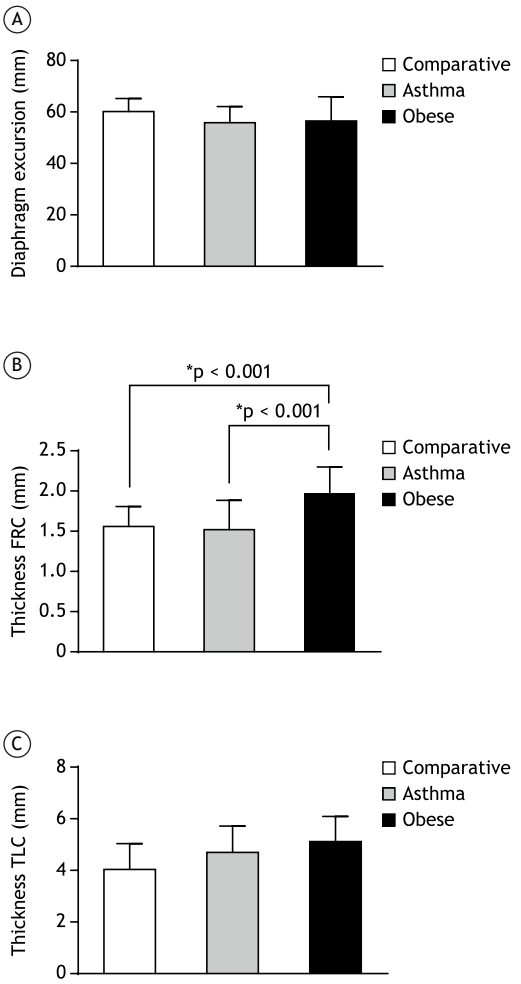

Figure 2. Comparison of diaphragm excursion (A), diaphragm thickness at functional residual capacity – Tfrc (B) and diaphragm thickness at total lung capacity -Ttlc (C), between obese group, asthma group and comparative group (59.6±9.8 vs 54.1±13.9 vs 53.7±16.3; p=0,4223, 1.6±0.2 vs 1.7±0.5 vs 2.0±0.4; p=0.001 and 4.3±1.2 vs 4.8±1.3 vs 5.2±1.2; p=0,0735, respectively). * One-way ANOVA with Tukey's multiple comparison test.

Table 1. Characteristics of the 73 adolescents.

Parameters	Obesity (n = 33)	Asthma (n = 26)	Comparative (n = 14)	p*
Age (y)	14(3.5)	14(3)	17.5(5.3)	>0.050
Total weight	83.3±17.8	47.2±10,4[a]	54.1±5,6[a]	**< 0.001**
Height	159±7,4	156±10,03	164±5,77	>0.050
BMIz-score	2.7(0.8)	0.52(0.1)[a]	-0.6(-0.8)	**< 0.001**
Lean Body Mass (Kg)	55.5±9.5	44.1±13.7[a]	44.9±4.5[a]	**< 0.001**
Fat Mass (Kg)	25.8±10.3	7.8±5.0[a]	8.5±4.3[a]	**< 0.001**
Body Fat (%)	30.8±7	14.6±8[a]	15.6±7.1[a]	**< 0.001**
Abdominal Circumference (cm)	99.9±12.8	68.6±13.6[a]	73±4.3[a]	**< 0.001**

Data are reported as median and interquartile range or mean ± standard deviation when applicable. BMIz-score: body mass index. [a]differences with obesity group. *One-way ANOVA with Tukey's multiple comparison test and Kruskall-Wallis test with Dunn's Multiple Comparison.

Systemic Leptin Levels and Adipokines Cell Culture

The obesity group had higher serum leptin levelsthan both the asthmatic and healthy groups [48.1(35.2) vs 10.1(16.9) vs 8.7(15.5), p<0.001]. The whole blood cell culture showed no significant differences of TNF-α and IL-6 responses to DPT and PHA among the three groups (Figure 3).

Table 2. Spirometric parameters of the adolescents.

Parameters	Obesity (n = 33)	Asthma (n = 26)	Comparative (n = 14)	*p**
FVC (%)	99.3±15.5	99.6±19.5	96.1±9.8	0,234
FEV1 (%)	96.3±15.2	91.6±18.2	95.1±9.7	0,497
FEV1/FVC	97.0±15,3	92,0±18,8	99,0±9,7	0,3309
MVV (%)	82.8±21.4[a]	72.5±21.2 [a]	102.8±27.3	**<0.001**
MIP (cmH_2O)	-76.2±25.7	-78.1±21	-72.2±20.5	0,745
MEP (cmH_2O)	86.2±24.5	80.3±27.2	79.9±25.2	0,601

FVC: percentage of predicted forced vital capacity, FEV1: percentage of predicted forced expiratory volume in one second, MVV%: percentage of predicted maximal voluntary ventilation, MIP – maximal inspiratory pressure; MEP: maximal expiratory pressure. The equations used to calculate predicted percentages were estimated by Pereira et al.[18]. [a]difference with comparative group. *One-way ANOVA with Tukey's multiple comparison test.

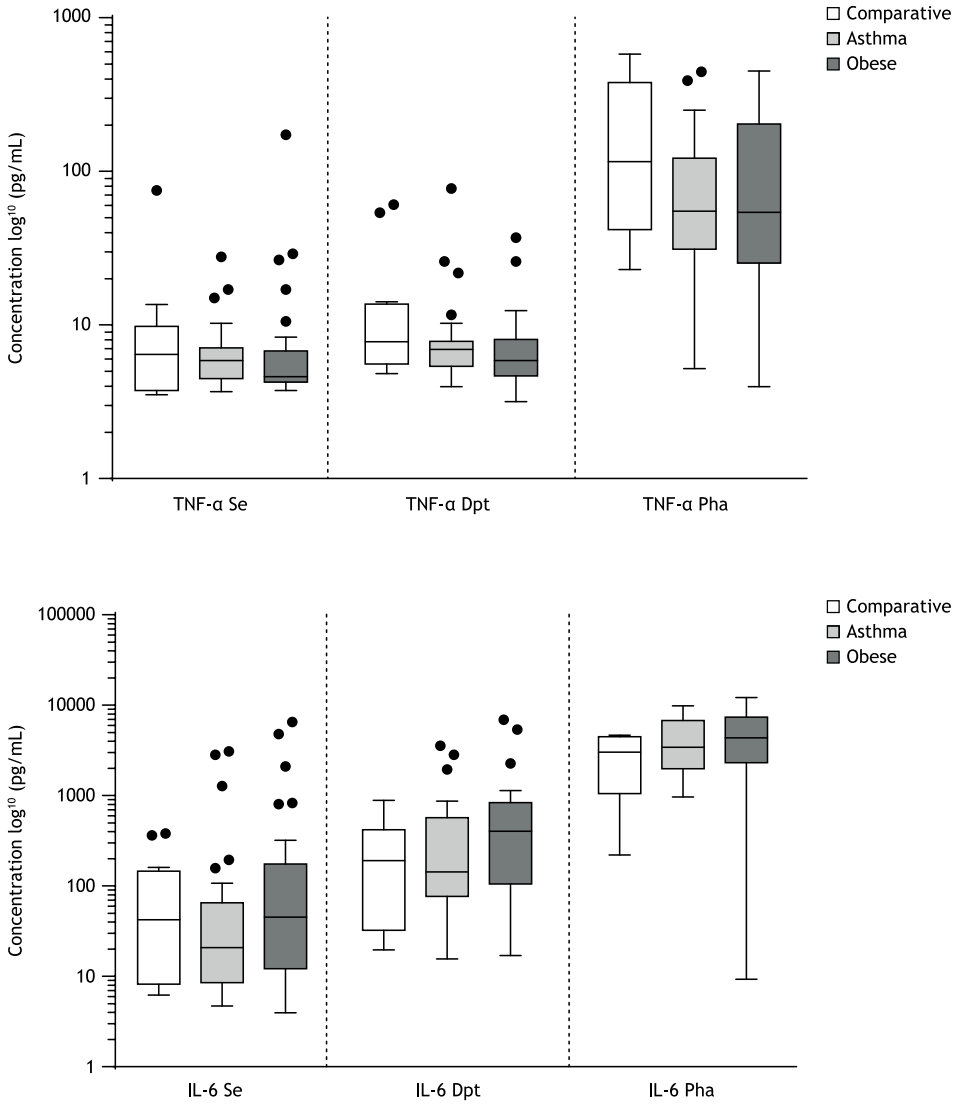

Figure 3. Comparison of (IL-6) and TNF-α levels in obesity, asthma and comparative groups. IL = interleukin, Se = no stimulus, Dpt = Dermatophagoides pteronyssinus, Pha = phytohemagglutinin.

DISCUSSION

This is the first study addressing the assessment of diaphragm excursion and thickness in a sample of obese and asthmatic young individuals with all measurements aimed at investigating the relationships with systemic levels of adipokines (leptin and IL-6) and TNF-α, spirometric variables and maximal respiratory pressures, mainly on diaphragm kinetics. We observed that obesity led to increased diaphragm thickness at functional residual capacity, but diaphragm excursion remained unaltered. Such hypertrophy can be justified by the increase in respiratory work imposed by the chronic condition of the disease. In controlled asthma, occasional asthma attacks did not cause an increase in muscle mass, although both the asthma and obesity groups had lower respiratory resistance than the healthy group. Neither the IL-6 nor TNF-α markers pointed to any evidence of muscle inflammation, altered leptin was expected in obese individuals.

We carried out different assessment of the diaphragm kinetics in youngsters. To our knowledge, only one previous study[21] had assessed sonographic measurements of diaphragmatic excursion and thickness in healthy infants and children proposing normal values for this age group. However, this study assessed the excursion and thickness of the diaphragm at functional residual capacity (FRC), failing to demonstrate the diaphragm dynamics.

Boussuges et al.[9] and Ueki et al.[16] clearly state the importance of assessing diaphragm excursion and thickness in total lung capacity (TLC). Until now, no previous studies had assessed sonographic measurements of diaphragmatic excursion and thickness in young obese individuals. Despite the reported difficulty in assessing excursion and diaphragmatic thickness in obese individuals,[9] our study found no difficulties in assessing diaphragmatic kinetics in obese youngsters.

The thickening of the diaphragm in its apposition zone may boost diaphragmatic excursion when facing an increase in physiological (maximum inspiration) or pathological (dyspnea) load in a well-awake patient.[22] Still, we also found a positive correlation between fat mass and body fat percentage with thickening fractions in the obesity group, allowing to conjecture that individuals with higher degrees of obesity may compromise diaphragm function. As we understand it, much still needs to be clarified about the behavior of diaphragm excursion, thickness, and thickening fraction in the context of obesity, especially regarding their impact on pulmonary function.

Some studies[23,24] have addressed the assessment of diaphragmatic kinetics with associated pathologies. In intensive care units, thickening fraction (TF) became a new index to predict diaphragm dysfunction.[25] It reflects the work of breathing settled by the diaphragm in response to a certain load and can replicate intrinsic diaphragm strength, but it is also influenced by the the load degree imposed to the respiratory system.[26] A higher TF may reflect increased breathing work in response to higher cardiorespiratory load imposed to the diaphragmatic muscle when assessed under spontaneous breathing conditions, but no upper limits are known for young individuals.[27]

Pulmonary function has been widely studied in the scope of obesity and asthma.[27] In this study, we found that both obese and asthmatic youngsters have normal pulmonary function, but decreased respiratory resistance (MVV) and showed normal values for maximal respiratory pressures. Recently, the white adipose tissue has been shown to control muscle metabolism and also contribute to the accumulation of intramuscular adipocytes, in addition to increasing insulin resistance.[28] This deposit of intramuscular fat may be detrimental to muscle function associated with the release of pro-inflammatory factors, such as leptin, IL-6, and TNF-α, which are harmful to muscle metabolism.[6]

Obesity and asthma have different responses to Th1 and Th2, influenced by the stimulant antigen and presence of cytokines in the environment.[7] In the context of obesidy, TNF-α is among the most studied pro-inflammatory cytokines.[29] It may be increased, but not necessarily implicated in inflammatory pathologies or processes. In our study, both the obesity and asthma groups had no significant response to TNF-α levels in relation to the comparative group, even upon DPT stimulation. This finding is consistent with other studies.[4,30] Serum IL-6 concentrations, known as low-grade chronic inflammatory markers, are associated with obesity and insulin resistance in both adults and children.[4,29] Smargiassi et al.[5] reported an association of circulating proinflammatory peptides, including CRP and IL-6, with abdominal adiposity, cardiometabolic risk factors, and insulin resistance in prepubertal children. Our findings the obesity group showed no significant response to IL-6 levels in any of the three stimulations in relation to the other groups. It is possible that the sample size in these variables was limited to identify the difference among the groups.

Thus, we based our hypothesis on the fact that high levels of serum leptin in obese individuals could be linked to changes in the diaphragmatic thickness, as shown in elderly populations in which leptin levels are associated with low physical performance and decreased strength and muscle mass.[6] We found significant differences in serum leptin levels in the obesity group, while leptin in the asthmatic group was similar to the comparative group. Nevertheless, our results shiw obese individuals with higher values of diaphragmatic thicknesses in FRC than the asthma and comparative groups. A possible explanation for these findings would be the accumulation of intramuscular adipocytes, although indirect inspiratory muscle training promoted by obesity should not be ruled out.[31]

Our patients were mild asthmatics who had normal pulmonary function in asthma attacks, therefore, no difference in lung function was present. We based our study on a hypothetical model in which a thickening of the diffragram and alteration in lung function would derive from fat accumulation in the liver resulting from chronic subclinical inflammation. However, our cell culture failed to demonstrate that these cytokines

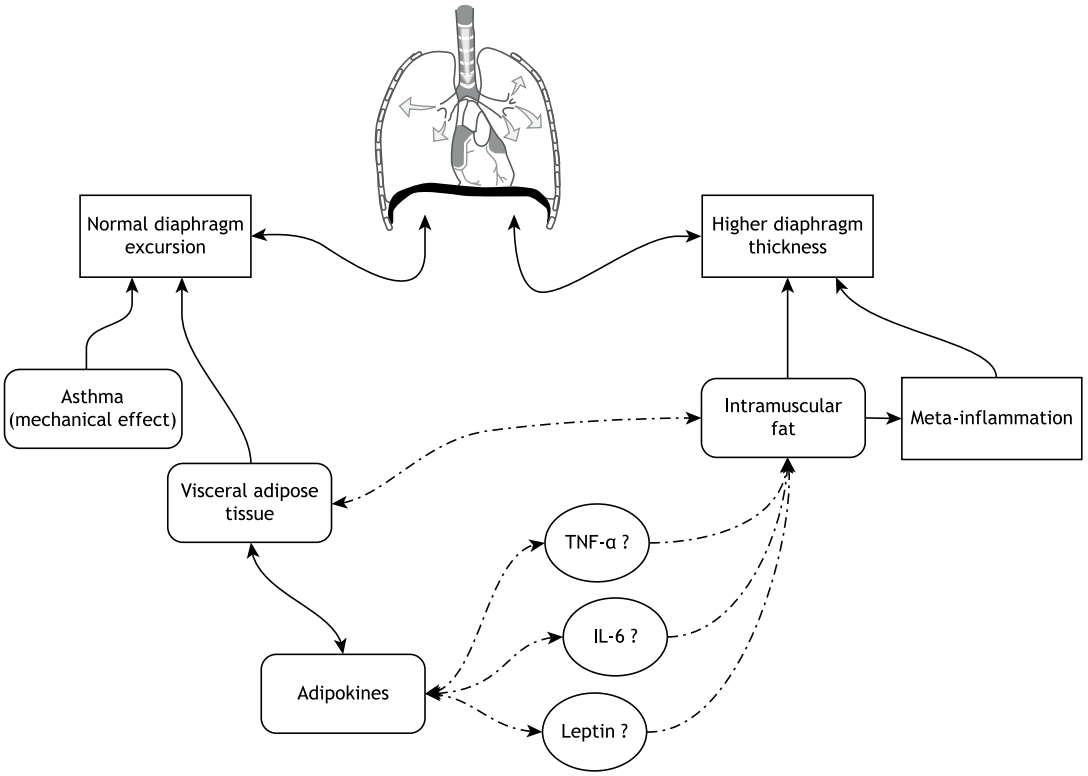

Figure 4. Conceptual model of obesity and asthma influence on diaphragm function. Note – IL – Interleukin. TNF – Tumor necrosis factor. ? – possible influence.

increase in muscle inflammation under allergic stimulus of dermpathophafoides pteronyssinus with significant increase in IL6 and TNF alpha, . The small sample size may have been the resason for such result (Figure 4).

Some limitations were involved in our study. Firstly, we assessed the diaphragm excursion and diaphragm thickness only on the right side, although the literature recommends it as the adequate area for being easily visualized. In addition, it has already been shown to lead to high reproducibility.[9] Secondly, we acknowledge that obesity has additional multiple risk factors that may affect diaphragm function (systemic inflammation, neuropathies, hypoxia, and drugs potentially involved with myopathy). Thirdly, hormonal influence of the airways, muscle development and lung maturation are confounding factors regarding gender and can affect the results. Seeking to minimize the influence of these variables, we decided that it would be beneficial to reach a balance in the distribution of male and female youngsters in the groups. Furthermore, although it seems that the age in the comparative group was more advanced, all adolescents had surpassed the first pubertal stage, in addition, when comparing the median values among the groups, no significant difference was found.

In conclusion, obese youngsters have greater thickness in FRC, but show no changes in diaphragmatic excursion. Although neither IL-6 nor TNF-a showed an increase, we should not relativize the role of leptin as an important pro-inflammatory adipokine, able to cause further repercussions in the diaphragm kinetics, differently from asthmatics and healthy individuals. In conclusion, this research introduces new possibilities for researchers to verify the effects of other adipokines and their role in skeletal muscle metabolism in obese or asthmatic young individuals, or both.

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AUTHOR CONTRIBUTIONS

Drs LHST, JAR and ESCS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr FCV and MSc HCMS designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Drs AFDA, VMBL, MAVCJ, GVAGL and DM conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Chronic thromboembolic pulmonary hypertension: the impact of advances in perioperative techniques in patient outcomes*

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ABSTRACT

Objectives: Pulmonary endarterectomy (PEA) is the gold standard treatment for chronic thromboembolic pulmonary hypertension (CTEPH). This study aimed at reporting outcomes of CTEPH patients undergoing PEA within 10 years, focusing on advances in anesthetic and surgical techniques. **Methods:** We evaluated 102 patients who underwent PEA between January 2007 and May 2016 at the Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo. Changes in techniques included longer cardiopulmonary bypass, heating, and cooling times and mean time of deep hypothermic circulatory arrest and shortened reperfusion time. Patients were stratified according to temporal changes in anesthetic and surgical techniques: group 1 (January 2007–December 2012), group 2 (January 2013–March 2015), and group 3 (April 2015–May 2016). Clinical outcomes were any occurrence of complications during hospitalization. **Results:** Groups 1, 2, and 3 included 38, 35, and 29 patients, respectively. Overall, 62.8% were women (mean age, 49.1 years), and 65.7% were in New York Heart Association functional class III–IV. Postoperative complications were less frequent in group 3 than in groups 1 and 2: surgical complications (10.3% vs. 34.2% vs. 31.4%, p=0.035), bleeding (10.3% vs. 31.5% vs. 25.7%, p=0.047), and stroke (0 vs. 13.2% vs. 0, p=0.01). Between 3 and 6 months post-discharge, 85% were in NYHA class I–II. **Conclusion:** Improvements in anesthetic and surgical procedures were associated with better outcomes in CTEPH patients undergoing PEA during the 10-year period.

Keywords: Pulmonary embolism; Pulmonary hypertension; Endarterectomy; Hospital mortality; Survival analysis; Postoperative complications.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe pulmonary vascular disease with high rates of morbidity and mortality.[1-3] CTEPH was recently recognized as a clinical condition, and its incidence following pulmonary embolism ranges between 0.6% and 3%.[4] Thus, pulmonary arteries are exposed to high pressures over a significant period of time, which influences the development of microvascular disease or secondary vascular arteriopathy.[5,6] The prognosis of this condition depends on the degree of associated right ventricular dysfunction and underlying pulmonary hypertension (PH). The 5-year survival rate of CTEPH patients without treatment is 30%, while the mean pulmonary artery pressure (mPAP) is between 40 and 50 mmHg. This rate is even lower, at approximately 10% when mPAP is above 50 mmHg, which highlights the severity of this disease and the need for effective therapies.[7,8]

Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH.[5,9-12] PEA surgically removes the obstructing thromboembolic material, resulting in significant improvements in right ventricular hemodynamics and function. In the past few years, adequate patient selection, advanced anesthetic, and surgical techniques and postoperative care have been associated with better outcomes in CTEPH patients.[5-8,11-13] Considering the evident learning curve for the operation and important changes in operative techniques over the years, the mortality rates have decreased from approximately 20% to 4% in reference centers for PEA.[5,6,9-15]

This study aimed at reporting the 10-year experience undergoing PEA in CTEPH patients referred to at a single university hospital in Brazil, emphasizing the influence of advances in surgical, perioperative, and postoperative outcomes, including survival rate within 2 years of follow-up.

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METHODS

Study design and participants

This was a retrospective study of CTEPH patients who underwent PEA between January 2007 and May 2016 at the Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InCor-HCFMUSP), a referral center for PEA. The protocol was submitted and approved by the Scientific Committee (Process No. 495631) of InCor-HCFMUSP. This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology initiative.[16]

The patient's selection followed predefined criteria for inclusion in this analysis: i) complete information in the electronic medical records, ii) both sexes and no age restriction, iii) CTEPH diagnosis, and iv) subjected to cardiopulmonary bypass (CPB) and in deep hypothermic circulatory arrest (DHCA) during surgical management. Patients were excluded if CTEPH was not confirmed during a surgical procedure.

Two improvements were made in the surgical techniques and were implemented over 10 years (Figure 1). The first was implemented in January 2013 and consisted of changes in the management of CPB and in the DHCA. The second was implemented in April 2015 and consisted of additional changes in the management of CPB and modifications in surgical and anesthetic techniques (Table 1). In this study, patients were stratified into three groups according to the period of time PEA was performed. Group 1 covers the period from January 2007 to December 2012 and includes 38 patients. Group 2 included 35 patients who underwent PEA between January 2013 and March 2015 after the first modifications in the surgical techniques were implemented. Group 3 included 29 patients who underwent PEA between April 2015 and May 2016 after the second modifications in the surgical techniques were implemented.

There was no calculation of the sample size, considering that all patients were included in the studied period.

Data collection

Data collection was performed using a database created in the Research Electronic Data Capture system. Regarding the preoperative phase, we collected clinical characteristics sucha as laboratory and imaging data, comorbidities, vascular staging, and hemodynamic parameters. In terms of the intraoperative phase, we collected CPB, DHCA, cooling and warming methods, reperfusion, and cardiac arrest time.

Clinical outcomes

Immediate outcomes after surgery, including mortality, were analyzed as 2-year survival rate and functional evaluation. Postoperative outcomes were defined as occurrence of complications[17-27] during the hospital stay.

Detailed description of the clinical outcomes is provided on the supplementary material.

Surgical techniques performed after April 2015 (group 3)

Surgical access was performed by median sternotomy to allow bilateral endarterectomy. CPB was installed after cannulation of the ascending aorta and superior and inferior venae cavae and progressive cooling up to 15°C with neuroprotection. Subsequently, a right pulmonary arteriotomy was performed to initiate thrombus dissection. Circulatory arrest was carried out in period limited to 20-min at a time, with reperfusion at 10-min interval.

Modifications to identify the adequate endarterectomy plane allowed surgeons to perform the operation on patients with thromboembolic disease in the distal segmental and subsegmental branches. After the endarterectomy on both sides, circulation with rewarming was started. During this maneuver, a right and left arteriorrhaphy was performed on the pulmonary arteries, followed by the resumption of the heartbeat. When the body temperature reached 36°C, mechanical ventilation and preparation for CPB disconnection were initiated. After CPB removal, hemostasis, pericardial drainage, and thoracotomy synthesis were performed. Once stabilized, the patient was transported to the ICU.

Anesthetic techniques performed after April 2015 (group 3)

During anesthesia induction, hypotension was prevented by using agents that were not associated with hemodynamic instability. Ketamine, fentanyl, and pancuronium were successfully used. Nitric oxide was started through mechanical ventilation at 10 p.p.m. Phenylephrine was preferentially prescribed as a vasopressor in these patients because of its effects

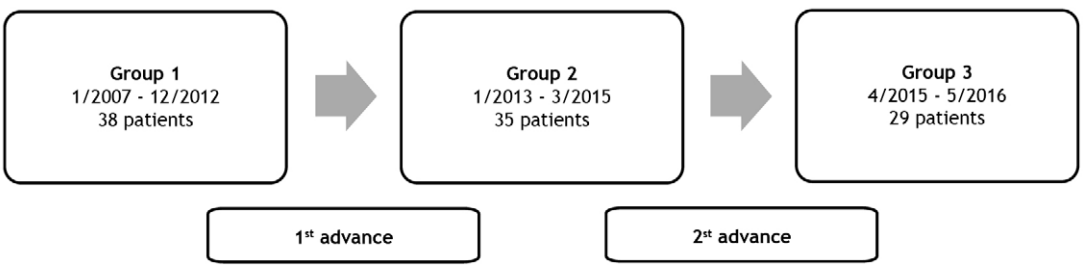

Figure 1. Study population stratified into groups according to time and advances in anesthetic and surgical techniques.

Table 1. Description of advances implemented during the study period.

Standardization of	1st improvement (January 2013)	2nd improvement (April 2015)
Cardiopulmonary bypass	• Cooling duration at least 70 min (up to 15°C) • Rewarm duration at least 90 min (up to 36°C)	• Reduction by half of the total volume of the dilutional prime • Invasive blood pressure monitoring in the radial artery • Temperature control with tympanic thermometer • Brain monitoring with BIS • Cooling jacket of the head after anesthetic induction
Deep hypothermic circulatory arrest	• Each period to up to 20 min • Reperfusion of 10 min between each DHCA	• None
Anesthetic procedure	• None	• Standardization of drugs in anesthetic induction • Hemodynamic control of PH with dopamine and phenylephrine • Femoral artery catheterization • Zero fluid balance (avoiding positive balance) • Use of transesophageal echocardiography • Use of Cell Saver® • Decrease in allogeneic transfusion
Surgical procedure	• None	• Cross-cannulation of the vena cava for the installation of CPB • Installation of a cannula for drainage of cardiac cavities • Use of thinner polypropylene yarns (6.0 and 7.0) for arteriorrhaphy • Use of biological glue after arteriorrhaphy

CPB: cardiopulmonary bypass; BIS: bispectral index; PH: pulmonary hypertension.

on right ventricular performance, maintaining CO, mean arterial pressure, and coronary artery perfusion.

During surgery, overhydration was avoided, using dynamic assessment of fluid status through the analysis of pressure pulse variation, echocardiography, and CO. We used Cell Saver, intravenous antifibrinolytic (aminocaproic acid during surgery), and goal-directed therapies such as prothrombin complex, fibrinogen concentrate, and platelet transfusion pending the diagnosis of the cause of bleeding, and red blood cell transfusion was rarely needed, but in cases with hematocrit <22% during CPB with signs of tissue hypoxia.

Detailed description of the anesthetic techniques performed is provided on the supplementary material.

Statistical analysis

Descriptive analysis of categorical data was expressed using absolute and relative frequencies to assess whether the groups were homogeneous. Differences between groups were evaluated using the chi-square test (Mantel-Haenszel). Analysis of variance or Kruskal-Wallis test was applied to analyze group differences. Continuous data were expressed as means and standard deviations.

Postoperative outcomes (surgical complications, infectious complications, and in-hospital mortality) were analyzed using univariate and multivariate logistic regression models. In this study, the parameters evaluated in the univariate model are presented in the supplementary materials.

After the univariate analysis, variables with $p<0.10$ were included in the multivariate logistic regression model (Tables 1S, 2S in the online-only data supplement). In the multivariate analysis, a value of $p<0.05$ was considered significant, and the odds ratio (OR) and 95% confidence interval (IC) were calculated. For the evaluation of in-hospital mortality, a Pearson correlation analysis was performed using the mPAP, pulmonary arterial systolic pressure (PASP), pulmonary vascular resistance (PVR), and CO. As PVR showed correlation ($p<0.010$) with mPAP, PASP, and CO, it was used in the multivariate model.

Survival analysis was calculated using the nonparametric Kaplan-Meier method, and the survival curves of the three groups were compared using the log-rank test, which was considered significant if $p<0.05$. Data were analyzed using SPSS for Windows version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics

A total of 110 patients underwent PEA during this period. We excluded eight patients: five were not confirmed as having CTEPH during surgery and three underwent a different surgical procedure. Therefore, we included a total of 102 patients in this study (Figure 1S in the online-only data supplement).

Of the 102 patients, 62.8% were female, and the mean age was 49.1 ± 14.8 years (Supplemental Table 1S). Of all patients who presented with dyspnea, 57.8% showed edema in the lower limbs, 33.3% had chest pain, 23.5% had syncope, and 7.8% had fatigue. Approximately 66% of patients were in New York Heart Association (NYHA) functional class III–IV. Previous single or recurrent pulmonary embolism was confirmed in more than 80% of the patients in each group, and a history of DVT was documented in more than 40% of patients. Thrombophilic disorder was diagnosed in 45 cases (44.1%).

Right ventricular catheterization indicated significant PH with elevated mPAP (mean, 53.2 mmHg and 53.2 ± 13.1 mmHg, respectively) and PVR (869.5 ± 380.2 dyn.s.cm^{-5}). No differences in clinical characteristics and hemodynamic parameters were observed among the three groups.

Surgery

Groups 2 and 3 had longer CPB time and longer cooling and warming time than group 1 (Supplemental Table 2S). In addition, groups 2 and 3 had longer DHCA time and a lower number of cardiac arrests than group 1. Information on the surgical classification of pulmonary vascular impairment (I to IV) was not available.

Postoperative outcomes

Surgical complications were less frequent in group 3 (10.3%) than in groups 1 and 2 (34.2% and 31.4%, respectively, p=0.035) (Table 2). Group 3 had a lower incidence of thoracic bleeding (10.3%) than groups 1 and 2 (31.5% and 25.7%, respectively, p=0.047) and a tendency toward less reoperation (10.3%) than groups 1 and 2 (29.0% and 17.1%, respectively, p=0.055). We also observed a tendency towards a lower incidence of neurological complications in group 3 (6.9%) than in groups 1 and 2 (22.8% and 26.3%, respectively, p=0.055) (Table 3). Patients in groups 2 and 3 presented with lower rates of stroke than those in group 1 (0 vs. 0 vs. 13.2%, p=0.01). No differences were observed between groups with respect to the occurrence of pulmonary reperfusion, acute kidney injury, or infectious complications.

The results of the multivariate analysis exploring variables associated with surgical complications, infectious complications, and in-hospital mortality are shown in Table 3. We found that being in group 3 was significantly associated with fewer surgical complications (OR 0.221 [95% CI 0.052–0.939], p=0.034 for the comparison of groups 1 and 3) and that high PASP was significantly associated with more surgical complications (OR 1.031 [95% CI 1.007–1.056], p=0.012). NYHA class III–IV was associated with more infectious complications than NYHA class I–II (OR 3.538 [95% CI 1.107–11.309], p=0.033).

Variables associated with higher in-hospital mortality were age (OR 1.06 [95% CI 1.02–1.10], p=0.047) and PVR (OR 1.00 [95% CI 1.00–1.01], p=0.024). From the receiver operating characteristic curve, after a partitioned analysis of the variables, patients aged ≥60 years were 6.2 times more likely to die and patients with PVR ≥860 dyn.s.cm^{-5} were 4.1 times more likely to die (Table 3).

Follow-up and 2-year mortality

Patients were evaluated 3–6 months after surgery, and >60% were in NYHA class I (Table 4). In the postoperative hemodynamic comparison, no significant difference was found in the parameters evaluated among the three groups. Of the 65 patients who underwent right heart catheterization, 58.5% developed residual PH.

The estimated survival probability at 24 months after surgery among the three groups was 70% for group 1, 77% for group 2, and 88% for group 3, and this difference was not significant (p=0.501).

Table 2. Postoperative outcomes.

Outcomes, n (%)	Group 1 (n = 38)	Group 2 (n = 35)	Group 3 (n = 29)	*P**
Pulmonary reperfusion edema	5 (13.2%)	3 (8.6%)	5 (17.2%)	0.674
Acute kidney injury	7 (18.4%)	2 (5.7%)	4 (13.8%)	0.497
Surgical complications	13 (34.2%)	11 (31.4%)	3 (10.3%)	**0.035**
Bleeding	12 (31.5%)	9 (25.7%)	3 (10.3%)	**0.047**
Pericardial effusion	3 (7.8%)	6 (17.1%)	2 (6.9%)	0.991
Reoperation	11 (29.0%)	6 (17.1%)	3 (10.3%)	**0.055**
Infectious complications	12 (31.6%)	8 (22.9%)	5 (17.2%)	0.173
Mediastinitis	4 (10.5%)	2 (5.7%)	1 (3.5%)	0.249
Septic shock	10 (26.3%)	7 (20.0%)	5 (17.2%)	0.363
Neurologic complications	10 (26.3%)	8 (22.8%)	2 (6.9%)	**0.055**
Delirium	6 (15.7%)	8 (22.8%)	2 (6.9%)	0.384
Stroke	5 (13.2%)	0 (0.0%)	0 (0.0%)	**0.010**
In-hospital mortality	9 (23.6%)	8 (22.9%)	3 (10.3%)	0.192

*P value from the chi-square test (Mantel-Haenszel); p<0.05 was considered significant; n total number of patients.

Table 3. Significant variables in the multivariate model for surgical and infectious complications and in-hospital mortality.

Variable	OR (95% CI)	*P*
Surgical complications		
Group		
G1	Reference	
G2	0.755 (0.250-2.275)	0.574
G3	0.221 (0.052-0.939)	0.034
Estimated PASP (mmHg)	1.031 (1.007-1.056)	0.012
Infectious complications		
NYHA class		
I/II	Reference	
III/IV	3.538 (1.107-11.309)	0.033
In-hospital mortality		
Age (years)	1.061 (1.018-1.105)	0.047
PVR (dyn.s.cm^{-5})	1.002 (1.001-1.003)	0.024

OR: odds ratio; PASP: pulmonary artery systolic pressure; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; p<0.05 was considered significant; CI confidence interval.

Table 4. Mid-term postoperative outcomes.

Variable	Group 1 (n = 29)	Group 2 (n = 27)	Group 3 (n = 26)	*P*
NYHA class, n (%)				0.385*
I	21 (75.0%)	16 (61.5%)	12 (63.1%)	
II	6 (21.4%)	9 (34.6%)	6 (31.5%)	
III	1 (3.5%)	1 (3.8%)	1 (5.2%)	
mPAP, mmHg (mean ± SD)	28 ± 9.7	30.4 ± 8.4	30.6 ± 14.3	0.661^{+}
RVP, dynas.s.cm^{-5} (mean ± SD)	248.3 ± 99.3	301 ± 257.6	317.7 ± 265.2	0.518^{+}
Residual hypertension, n (%)	13 (50%)	16 (72.7%)	9 (50%)	0.852*
Pulmonary vasodilator therapy, n (%)	1 (3.4%)	1 (3.8%)	2 (9.5%)	0.367*

NYHA: New York Heart Association; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance. *P value from the chi-square test (Mantel-Haenszel); $^{+}$P value from analysis of variance (ANOVA); n, patients with assessment; p<0.05 was considered significant.

DISCUSSION

The surgical treatment of CTEPH at InCor-HCFMUSP in Brazil started in 1981,[28] but only after 1990 that the operations were performed by the same surgical team. Within 10 years, the procedures were standardized, and this study analyzed the data of that period (from 2007 to 2016) and evaluated the influence of the interventions implemented on the procedures and their outcomes.

We had four main findings. First, we observed that surgical complications were less frequent after additional advances in surgical techniques were implemented. Thoracic bleeding occurred less in group 3 than in groups 1 and 2, and there was a tendency toward less reoperation and neurologic complications. Second, beyond being in group 3, we observed that high PASP was significantly associated with more surgical complications, and a higher NYHA class was associated with more infectious complications. Third, increasing age and PVR were significantly associated with in-hospital mortality. Finally, >60% of patients were in class I 3–6 months after surgery, but we did not observe differences in estimated survival probability among groups.

PEA remains the gold standard for CTEPH, and one of the factors that influence the post-surgical result is the experience of the referral center in disease management. The experience of clinicians, surgeons, and radiologists is essential for providing correct surgical indication, total removal of thromboembolic obstruction, and accurate management of the immediate and late postoperative period.[7,29,30] This level of experience was acquired by the local team at InCor-HCFMUSP, which probably also influenced the positive results of this study.

As CTEPH rarely occurs and difficult to diagnose, only a few specialized centers exist worldwide. The most important centers are found San Diego (USA), United Kingdom, France, and Germany (Europe).[15,29] In the last few years, some centers have disclosed their postoperative results,[5,6,9-15] which has helped

us improve management by surgical, clinical, and postoperative teams.

In our study (10-year period), patients undergoing PEA in different time periods had similar baseline characteristics, clinical presentation, and functional and hemodynamic parameters. Approximately 50% of CTEPH patients had multiple risk factors the most frequent of which were smoking (20%), chronic venous insufficiency (13.7%), family history of venous thromboembolism or pulmonary embolism (10.7%), and these main variables were included in our univariate analysis. Their rates were comparable with those reported by Cannon et al.[15] and Pepke-Zaba et al.,[29] except for smoking, which was not mentioned. Significant PH was observed, with high mean values of PVR and mPAP, similar to previous reports.[12,15] During surgical procedures, the increase in total CPB time resulted from the standardization of the cooling, warming, and reperfusion times in groups 1 and 2. Thus, there was a progressive and significant increase in the cooling and warming times, and a reduction in the total systemic reperfusion time was probably associated with lower number of DHCA. Decreasing the number of DHCA was possible by increasing the mean time of each DHCA, allowing the safe removal of accessible thrombi from the pulmonary arteries. Previous studies[9,10] have shown advances in surgical techniques and in anesthetic procedures similar to those performed in our center, which also yielded improved outcomes.

Regarding surgical complications, operative field bleeding decreased significantly over time, similar to data from other authors.[12] In the multivariate analysis, being in group 1 was significantly associated with more surgical complications than being in group 3, which suggests the effectiveness of strategies for improvement such as the use of thinner polypropylene wires to perform arteriorrhaphy and biological glue. High preoperative PASP was associated with increased incidence of surgical complications, which may be related to the high pressure in damaged vessels and a higher incidence of bleeding. Note that the non-invasive measurement of PASP was performed up to 3 months from the date of surgery (84.67 ± 120.46 days), and invasive measurement of pulmonary pressures by right ventricular catheterization was performed after 3 months from the date of surgery (107.06 ± 194.03 days). Improvements in the arteriorrhaphy technique probably contributed to the lower occurrence of surgical complications. Regarding neurologic complications, stroke occurred in five patients in group 1, but not in groups 2 and 3. The results showed that the longer the DHCA time, the greater the incidence of temporary neurological complications.[12] In our study, the DHCA time did not reduce over time, but we observed an increase in the mean DHCA time with lower number of DHCA, which could have contributed to less permanent neurological complications, an original finding of this study. Additionally, the mortality rate in our center was comparable with that of previous studies that showed rates from 4.4% to 16%.[2,9,10,12,15] In our study, higher age and PVR were associated with in-hospital mortality, which might be explained by the development of microvascular disease and/or secondary vascular arteriopathy, contributing to worsening hemodynamic status and poorer prognosis after surgery.[5,6,10,11,13,14]

The postoperative functional evaluation through clinical evaluation at 3–6 months after hospital discharge showed that >94% of the patients were in functional class I–II, suggesting significant clinical improvement.[5,10,12,15] Although no significant differences were observed among the three groups in relation to hemodynamic parameters postoperatively, there was an important improvement in these values when compared with the preoperative values, similar to previous reports.[15]

We acknowledge two significant limitations of our study. First, as an observational single-center retrospective study, unmeasured confounding is always present, and our results should be interpreted as hypothesis-generating research. Second, improvements were performed in progressively reduced time intervals (60, 26, and 16 months for groups 1, 2, and 3, respectively); however, the number of PEA operations was similar among these time periods. These data revealed that a greater number of surgeries were performed with the same time interval (group 1, 0.6 surgeries/month; group 2, 5.9 surgeries/month; group 3, 1.8 surgeries per month).

Within the 10-year period, the InCor, a well-known Brazilian referral center for PEA surgery, promoted advances in anesthetic and surgical techniques, which are associated with a lower occurrence of surgical and postoperative complications. Further advances in the field are expected to progressively increase the quality of life and survival rate after this procedure.

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AUTHOR CONTRIBUTIONS

PGS: collaborated in the idealization of this work, construction of the database, data collection, data analysis, drafting the article and reviewing it. MT-F: collaborated in the direction of this work, from initial ideation to the final revision of Article. OFF: collaborated in the construction of the new surgery protocol, performing the surgeries, in the construction of the database, analysis and review of the article. TDA: collaborated in database construction, data analysis and revision of Article. DON: collaborated in the standardization of data collection and in the data collection itself. LMG: collaborated in data collection. FAG: collaborated in the construction of the new surgical protocol and in performing the surgeries using the new protocol. LAH:

collaborated to write the article and review it. FRBGG: collaborated in the construction of the new surgical protocol and in the anesthesia of the operated cases. FBJ: collaborated in the idealization of this work, construction of the database, data analysis, drafting the article and reviewing it.

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Respiratory symptoms (COPD Assessment Test and modified Medical Research Council dyspnea scores) and GOLD-ABCD COPD classification: the LASSYC study

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Study carried out in the Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, and Uruguay.

ABSTRACT

Objective: To assess the frequency and severity of 24-hour respiratory symptoms according to COPD GOLD-ABCD classification (2017-version), the distribution of the patients with COPD into GOLD categories using mMRC (≥2) or CAT (≥10) scores, and agreement between these cut-off points. **Methods:** In this cross-sectional study (LASSYC study), 24-hour day respiratory symptoms were assessed by the Evaluating Respiratory Symptoms in COPD (E-RS) questionnaire, Nighttime Symptoms of COPD Instrument (NiSCI), Early Morning Symptoms of COPD Instrument (EMSCI), CAT and mMRC scores. **Results:** Among the 734 patients with COPD, 61% were male, age 69.6±8.7 years, FEV_1% post-BD 49.1±17.5%, mMRC 1.8±1.0 and CAT 15.3±.8.1. By mMRC 33.7% were group-A, 29.2% group-B, 10.2% group-C and 26.9% group-D. By CAT 22.3% were group-A, 41% group-B, 4.8% group-C and 31.9% group-D. Using the mMRC the severity of E-RS, NiSCI and EMSCI scores increased from group A to D. Using the CAT, the groups B and D had the higher scores. Agreement between mMRC and CAT was 89.5% (Kappa statistics=75.7%). For mMRC score of 2, CAT score of ≥11 showed the maximum Youden's index (1.34). For mMRC score of 1, CAT score of ≥9 and ≥10 showed the maximum Youden's index (1.48). **Conclusion:** GOLD COPD classification by CAT seems to better discriminate 24-hour symptoms. Results do not support the equivalent use of CAT≥10 and mMRC≥2 for assessing symptoms.

Keywords: Chronic obstructive pulmonary disease; Symptoms and COPD.

INTRODUCTION

The "ABCD" COPD assessment tool proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[1] is based on the combination of the patient's level of respiratory symptoms, and future risk of exacerbations. Spirometry is needed for diagnosis and extent of airflow limitation. To evaluate the symptoms, the GOLD document recommends the use of the modified British Medical Research Council dyspnea scale (mMRC) or the COPD assessment test (CAT) in an equivalent manner.[1]

The mMRC scale has been considered to be an adequate unidimensional tool for symptoms assessment in COPD due to its relationship with other health status measures and prognostic value.[2,3] It is recognized that COPD impacts patients beyond dyspnea,[4,5] therefore a comprehensive and multidimensional rather than a unidimensional assessment of symptoms is recommended. For this reason, and for its predictive value on important COPD outcomes, the CAT score has been proposed as a surrogate tool for assessing symptoms in COPD.[6-11]

We have previously reported that in patients with COPD the mMRC and CAT scores progressively increased as the intensity of daytime symptoms worsen (from mild to severe), and there was a relationship between daytime symptoms with mMRC and the CAT scores.[12] However, to our knowledge, no information exists regarding the presence of symptoms along the 24-hour day in patients classified in the different GOLD-ABCD subgroups using CAT or mMRC scores.

On the other hand, several reports have indicated that the GOLD group assignment of patients with COPD is different depending on the scale of symptoms used.[13-22] Although a simple breathlessness cutoff-point cannot be equated to a comprehensive or a full symptom score cutoff, and patients with mMRC <1 may also have a number of other COPD symptoms,[23] the use of the mMRC is widespread, and mMRC of ≥2 as a threshold

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for separating "less breathlessness" from "more breathlessness" is used together with a CAT ≥10 into the GOLD assessment tool. Controversies remain regarding the ideal CAT score cutoff-point equivalent to an mMRC value or the extent of agreement between the two scores.[24]

The **L**atin **A**merican **S**tudy of 24-hour **Sy**mptoms in **C**hronic Obstructive Pulmonary Disease (LASSYC) describes prevalence, severity and inter-relationship of early morning, day and night-time symptoms in patients with COPD recruited from clinics[12]outpatients. This study offers an opportunity to explore the distribution of respiratory 24-hour day symptoms according to the GOLD categories using the mMRC or CAT scores in a large sample of stable patients. Therefore, the main objective of the present study was to determine the frequency and severity of the 24-hour day symptoms according to GOLD-ABCD classification by mMRC and CAT scores. We also assess the distribution of the patients with COPD into each of the GOLD-ABCD categories by using the recommended mMRC or CAT scores cutoff-points (CAT ≥10 or mMRC ≥2), and analyze the agreement between the assigned patients into GOLD-ABCD categories using the GOLD cutoff-points.

METHODS

The LASSYC was a prospective observational, multicenter, multinational, cross-sectional, non-interventional study (Clinical Trial Registration: NCT02789540), in patients with COPD from seven Latin American countries: Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, and Uruguay.[12] The main objective of the original study was to describe prevalence, severity and inter-relationship of early morning, day and night-time symptoms with COPD severity, exacerbations and patient reported outcomes (PROs) in stable patients.

A total of 795 patients with COPD were enrolled distributed among specialists in respiratory medicine in the selected countries. Each country recruited between 100-130 patients and each site around 10-15. The recruitment was competitive inside each country after the expected site recruitment time of one month, up to total of three months recruitment period. The study was approved by the ethics committees for each site and all patients provided written informed consent.

The methodology of the study has been previously[12,25] described; briefly, outpatients ≥40 years of age with a diagnosis of COPD for at least 1 year, at least one spirometric value with a COPD diagnosis using the post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.70 criteria in the previous 12 months, current or ex-smokers (≥10 pack-years), stable disease (without treatment for an exacerbation or changes in current treatment in the previous 2 months) were included in the study.[12,25] Patients with a diagnosis of sleep apnea or any other chronic respiratory disease, any acute or chronic condition that would limit a patient's ability to participate in the study were excluded.

The following information was collected for each patient: social demographics, health insurance system, lifestyle, smoking history, presence of comorbidities, level of dyspnea, disease severity, prescribed COPD treatments, exacerbation history, and healthcare resource utilization during the last 12 months. The level of dyspnea was measured using the mMRC scale[2] and the CAT score was used to evaluate the impact of the disease.[6]

COPD classification was performed according to the GOLD-ABCD categories (2017-version) using the CAT and mMRC scores separately.[1] The patients were categorized into GOLD-ABCD groups twice with mMRC or CAT score for symptom assessment, respectively.

Assessment of 24-hour day respiratory symptoms (early morning, daytime and night-time symptoms)

"Evaluating Respiratory Symptoms in COPD" E-RS™ 2016 (formerly EXACT-RS)[26] was used to assess daytime symptoms. The night-time and early morning symptoms were assessed with the Nighttime Symptoms of COPD Instrument (NiSCI) and Early Morning Symptoms of COPD Instrument (EMSCI).[27-29] A detailed explanation of the methodology used in the study for the evaluation of 24-hour day respiratory symptoms and the validation of the instruments in Spanish have been previously[12,30] described.

Briefly, dichotomous variables for defining daytime, early morning and night-time symptoms were built. For daytime symptoms, the third tertile of the score were considered daytime symptoms; the early morning symptoms were defined according to the severity of dyspnea, classified as moderate or higher, added to other symptoms, classified as moderate or more severe; for night-time symptoms, we considered those who woke up at least once at night due to COPD symptoms.

Statistical analysis

Descriptive statistics included the absolute and relative frequencies for categorical variables and mean and standard deviation for numerical ones. No individual was excluded in the analysis.

We calculated the agreement of the GOLD-ABCD classification of COPD for the CAT and mMRC scales thresholds using Kappa statistics (weighted and unweighted). Also, we calculated the area under curve for the CAT score, using as reference the mMRC scale ≥ 2 drawing the graph. Sensitivity, specificity, positive (PPV) and negative (NPV) predicted values

for each of the cut off points in the mMRC scale were calculated with their respective 95% confidence interval. Additionally, the Youden's index ($\frac{sensitivity + specificity}{100}$) was calculated to establish the best value of the CAT score related to the mMRC scale.

We considered a p-value less than 5% as statistically significant. All analyzes were performed using Stata 13.1 (StatCorp LP, 2013. Stata Statistical Software: Release 13. College Station, TX, USA).

RESULTS

A total of 795 patients were included between May and August 2016, 61% were male with a mean age of 69.5±8.7 years, a mean post-bronchodilator FEV_1 of 49.1±17.5% of predicted mMRC score of 1.8±1.0 and 15.2±8.2CAT score . The general characteristics of the overall patient population and by country has been published elsewhere.[31]

The Figure 1 shows the patient's assignment into GOLD-ABCD categories using the CAT score cutoff-point ≥10 and the mMRC scale cutoff-point ≥2. When classification was performed according to mMRC scale the distribution (%) of patients in the ABCD groups were 33.7%, 29.2%, 10.2% and 26.9%, respectively; on the basis of the CAT score the distribution was 22.3%, 41%, 4.8% and 31.9%, respectively. When the stratification of symptom was done by CAT score, the proportion of high symptom groups (B and D) was increased.

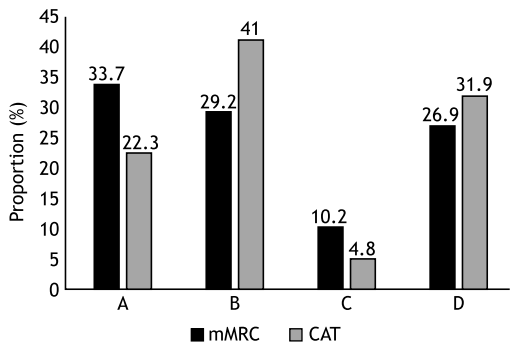

Figure 1. Patient's assignment into GOLD-ABCD categories using the CAT score cut point ≥10 or the mMRC scale cut point ≥2.

The frequency of the 24-hour day respiratory symptoms according to GOLD-ABCD classification by mMRC and CAT scores is shown in the Figure 2. The frequency of 24-hour day symptoms in all COPD categories is low reaching less than 50% of patients in the most severe group D.

The Figures 3-5 show the E-RS, NiSCI and EMSCI symptoms severity scores according to GOLD-ABCD classification by the mMRC and CAT scores, respectively. When the GOLD-ABCD classification was performed by using the mMRC scale, the severity of the symptoms scores E-RS, NiSCI and EMSCI progressively increased from GOLD groups A to D. In contrast, when the CAT score was used, the groups B and D were those with the higher scores. According to the definition of symptomatic patients by the E-RS score (10 units distinguish less vs. more symptomatic patients) when the GOLD-ABCD classification was performed by using the mMRC scale the mean score of patients in the groups B, C and D classified them as highly symptomatic, and those in group A as mild symptomatic. Using the CAT score only the patients in the groups B and D were classified as highly symptomatic and those in the group A and C as mildly symptomatic.

The agreement between the assignment of the patient into GOLD categories using the CAT score cutoff-point ≥10 and the mMRC scale cutoff-point ≥2 is shown in Table 1. The observed agreement for the GOLD groups by CAT and mMRC scores was 89.5%

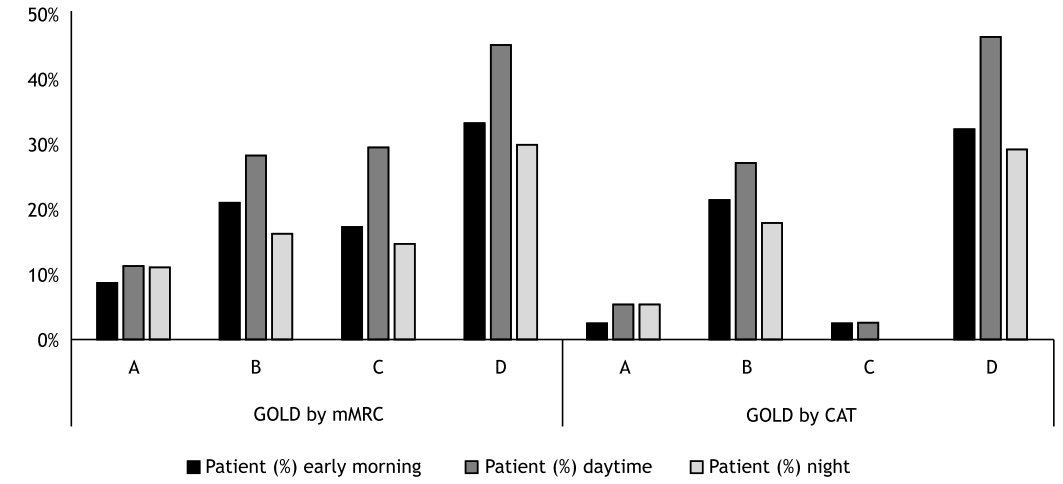

Figure 2. Frequency of the 24-hour day symptoms according to GOLD-ABCD categories by mMRC scale and CAT score.

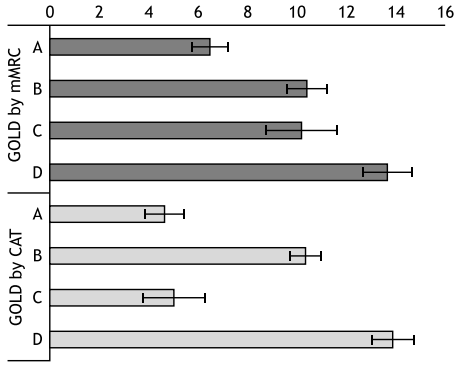

Figure 3. Daytime symptoms (E-RS) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

(Kappa statistics= 75.7%), suggesting a substantial but not identical agreement (Table 1).

The agreement between mMRC and CAT scores for each cutoff-point is shown in Supplementary Table S1. For an mMRC score of 2, a CAT score of ≥11 showed the maximum Youden's index value (1.34) with a sensitivity and specificity of 84.8 and 49.3, respectively (AUC 67.1; 95%CI 63.9-70.2). For mMRC score of 1, a CAT score of ≥9 and ≥10 showed the maximum Youden index values (1.48). The sensitivity and specificity for the CAT score ≥9 were 80.8 and 67.3 (AUC 74.0; 95%CI 67.6- 80.5), respectively, and for the CAT score ≥10 the sensitivity and specificity were 77.4 and 70.9 (AUC 74.2; 95%CI 67.9- 80.4), respectively. Supplementary Figure S1 shows the

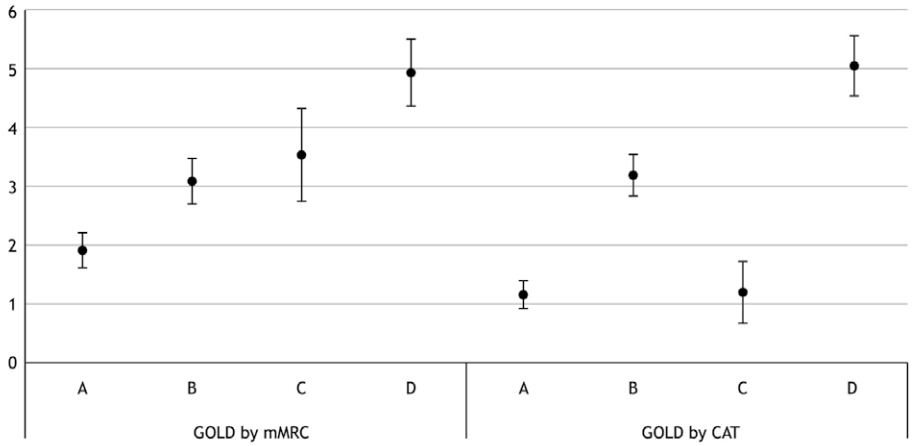

Figure 4. Early morning symptoms (EMSCI) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

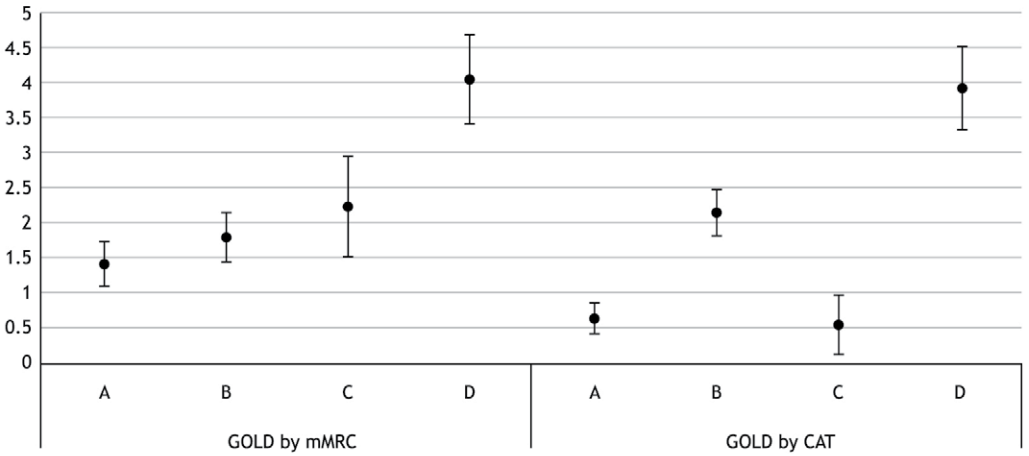

Figure 5. Night-time symptoms (NiSCI) severity score according to GOLD-ABCD classification by the mMRC scale and CAT score.

Table 1. Agreement between patient's assignments into GOLD categories using the CAT score cut point ≥10 or the mMRC scale cut point ≥2.

		CAT classification							
		A	B	C	D	Weighed analysis		Unweighted analysis	
						Observed agreement (%)	Kappa statistics	Observed agreement (%)	Kappa statistics
mMRC	A	140 (17.6)	128 (16.1)	0 (0.0)	0 (0.0)	89.5	75.7	69.2	56.9
	B	34 (4.3)	198 (24.9)	0 (0.0)	0 (0.0)				
	C	1 (0.1)	0 (0.0)	19 (2.4)	61 (7.7)				
	D	2 (0.3)	0 (0.0)	19 (2.4)	193 (24.3)				

ROC curve for the CAT score discriminating power for each cutoff-point of mMRC score. For a mMRC score ≥1 and ≥2, the AUC was 0.83 and 0.74, respectively, indicating that the CAT score had a better discriminating power for mMRC grade ≥1.

DISCUSSION

The main findings of this study on respiratory symptoms and GOLD-ABCD COPD classification in patients from Latin America were: first, the distribution of the patients with COPD into the GOLD categories by the mMRC or CAT scores is not equal, showing the stratification of symptoms by the CAT score a greater proportion of patients in the groups with high symptoms (B and D); second, the GOLD-ABCD classification by CAT score seems to better discriminate 24-hour day symptomatic patients than mMRC scale and third, the use of a mMRC score of 1 with a CAT score ≥10, and a mMRC score of 2 with a CAT score ≥11 seem to be in our population the best thresholds to make CAT and mMRC equivalent.

Several studies have reported differences in the patient's distribution into the GOLD-ABCD categories by using the scores of CAT ≥10 or mMRC ≥2.[13-22] Karloh et al.[24] performed a systematic review and meta-analysis about classification of patients into GOLD categories by CAT ≥10 or mMRC ≥ 2 scores based on the data of 10 studies. By using the mMRC scale the proportion of patients into the groups ranged from 20.3-53% (average 32%) in group-A, 6.8-24.7% (average 16%) in group-B, 5-36.7% (average 20.4%) in group-C, and 12-38.2% (average 31.6%) in group-D; by using the CAT score the proportion into the groups ranged from 5-34.3% (average 18.8%) in group-A, 19.2-48.5% (average 29.7%) in group-B, 0.7-19.8% (average 7.8%) in group-C, and 20-63.3% (average 44.1%) in group-D.[23] In all studies, the proportion of groups with high symptoms (B and D) increased when the stratification of symptoms was done by using the CAT score.[24] On average, the distribution was 13% different according to the instrument used. Another study showed that the most frequent discrepancy was to have a low level of dyspnea but a high CAT score, which in according with the authors opinion may be explained by variables impacting health status but with little impact on dyspnea, such as depression, anxiety or frequent exacerbations.[32]

The results of the present study are consistent with those reported in other populations showing that the proportion of patients categorized into groups A to D differed according to the use of a GOLD symptom cutoff-point of mMRC ≥2 or CAT score ≥10, therefore the choice of symptom scale can alter the group assignment in the GOLD-ABCD classification because mMRC and CAT scores do not behave in the same way in distinguishing symptom groups. These finding support the concept that the CAT and mMRC scores are not equivalent for the purpose of assessing the patients symptoms.

The symptoms of COPD vary throughout the 24-hours a day, so there is a growing interest in evaluating the patterns of 24- hours a day. Some authors suggest that the therapy adapted according to the pattern of the 24-hours a day symptom could provide important benefits in the management of patients with COPD.[33] According to the E-RS score a symptomatic patient is usually defined as the one having at least ten units in the score. This threshold was selected based on evidence suggesting that 10 units could distinguish between less symptomatic (GOLD groups A and C) and more symptomatic (GOLD groups B and D) patients.[34,35]

Results from an observational study in Europe have shown that more than 50% of patients with COPD report respiratory symptoms during the 24-hour day.[30] In addition, it showed a relationship between the 24-hour day symptoms and worse patient-reported outcomes.[30,36] We have previously reported the frequency of respiratory symptoms during the 24-hour day in patients with COPD from Latin America.[12] The frequency of the 24-hour day symptoms in our population was lower (20% and 18%) compared with others[5,30,37]. The study also showed that mMRC and CAT scores progressively increased as the intensity of daytime symptoms worsened (from mild to severe), and there was a strong correlation between E-RS global score with mMRC and the CAT score ($r=0.715$; $p<0.001$).[12]

To our knowledge, no previous study has evaluated the distribution of respiratory 24-hour day symptoms according to the GOLD-ABCD categories, as well as the differences in the frequency and severity of these

symptoms when GOLD stratification of the symptoms was performed using the mMRC or CAT scores.

The results of the present study show that the GOLD-ABCD classification by using the CAT score seems to better discriminate the more symptomatic patients (group B and D) by showing an E-RS score higher than 10 units only in the GOLD symptomatic groups B and D, and below this threshold in the low symptomatic groups A and C. In addition, the results expand the findings of other studies that demonstrate the predictive ability of CAT score on important COPD outcomes such as exacerbations, and mortality.[7-11] Interestingly, the GOLD-2019 document uses the multidimensional scores CAT to categorize patients as highly symptomatic in the high-risk group D (CAT ≥20) recommending the initial treatment with two bronchodilators, thus suggesting a central role of the CAT score for patients classification. Therefore, new classification schemes should be benchmarked against CAT score.

The agreement between CAT (≥10) and the (mMRC ≥2) to categorize patients into the GOLD classification system is another controversial issue. The results of a meta-analysis based on the data of 8 studies[13-21] indicate that using these cutoff-points the agreement between CAT and mMRC ranged from poor to substantial (k-coefficients between 0.13 to 0.77) with a pooled k coefficient of 0.548 (95% CI, 0.35-0.70; p< 0.0001) and high heterogeneity among the studies (I^2=99.3; z= 4.84). As a consequence of these, some authors have suggested using the cutoff-point for mMRC score of ≥1 rather than ≥2, for showing this the highest concordance (k-coefficient 0.66-0.79) with a CAT cutoff-point score of ≥10.[38]

Another study showed that a CAT score of ≥10 had 82% sensitivity but 24% specificity to identify mMRC grade ≥2, while a score of 17 had 98% specificity but a low sensitivity of 52% and did not improve the agreement.[39] The authors recommend that using mMRC ≥2 and CAT score ≥17 to identify more symptoms would avoid discordant categorization which is also consistent with the schema for exacerbation risk assessment.[39] Other authors performed a pooled analysis in order to find the best fitting cutoff-points for GOLD symptom measures, with a mMRC dyspnea grade of ≥2 as the point of reference in a total of 18,577 patients with COPD.[40] The results indicate that using mMRC ≥2 points as a reference, a CAT cutoff-point of ≥18 points reached the highest agreement.[40]

Our results are in line with previous studies[13-21] showing that the observed agreement for the GOLD groups by CAT score ≥10 and the mMRC ≥2 was substantial but not identical and that a mMRC score of 1, with a CAT score of ≥9 and ≥10 showed the maximum Youden's index value with an AUC of 74.0 and 74.2, respectively.[14,38] This approach would probably improve the patients being classified into the same GOLD group regardless of the instrument used for symptom assessment and avoid differences in a patient's management, including the choice of the appropriated pharmacological therapy.

This study has some limitations that should be mentioned. Despite the study includes a large number of patients with COPD from seven countries, is not possible to conclude that this sample is representative of the entire COPD population from Latin America; however, the sample included patients with different GOLD-ABCD categories and may provide a valid estimation of patients characteristics from the region. Finally, the definitions of severity of daytime symptoms and of "significant" morning and night-time symptoms are arbitrary as no universally accepted definitions exist. Therefore, the proposed definitions identified patients with different degrees of impairment and different outcomes. Although the use of questionnaires is the only way to investigate the frequency and severity of symptoms, their interpretation may be subjected to bias.

In conclusion, our results do not support the equivalent use of a CAT score of ≥10 and mMRC ≥2 for the purpose of assessing patient symptoms in the GOLD-ABCD classification. The GOLD-ABCD classification by CAT score seems to better discriminate the more 24-hour day symptomatic patients than mMRC scale.

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AUTHOR CONTRIBUTIONS

MMO, MVLV, AMBM, FCW, LR and MM, contributed substantially to the study design, data collection, interpretation, and reviewed the manuscript. AMBM and FCW performed the data analysis while all authors were involved with data interpretation. MMO wrote the manuscript. All authors approved the final version of the manuscript and agreed to its submission to Respiratory Medicine.

CONFLICTS OF INTEREST

MM has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Laboratorios Esteve, Ferrer, Gebro Pharma, GlaxoSmithKline, Grifols, Menarini, Mereo Biopharma, Novartis, pH Pharma, Rovi, TEVA, Verona Pharma and Zambon, and research grants from GlaxoSmithKline and Grifols. AMBM has received consulting fees from AstraZeneca for the statistical analysis of the LASSYC study. MMO, MVLV, and FCW: no real or perceived conflicts of interest. Larissa LR: Employee of AstraZeneca.

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ORIGINAL ARTICLE

The high-risk factors of different severities of bronchopulmonary dysplasia (BPD) based on the national institute of child health and human development (NICHD) diagnosis criteria in 2018

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ABSTRACT

Objective: To investigate the clinical characteristics of preterm infants with different severities of bronchopulmonary dysplasia (BPD) and disclose the high-risk factors of exacerbating BPD. **Methods:** Collection of clinical data of 91 preterm infants admitted to the NICU and diagnosed with BPD, categorized in groups according to the disease severity: 41 mild cases,, 24 moderate cases, and 26 severe cases. Comparison and analysis of perinatal risk factors, treatment, complications and prognosis of the infants with different severity degrees. **Results:** The severe group had a higher proportion of infants with congenital heart disease (CHD) higher than the moderate group ($P < 0.05$), and a higher ratio of pneumonia and mechanical ventilation (MV) ≥ seven days than the mild group ($P < 0.05$). The severe group also presented higher reintubation incidence than both the mild and moderate groups ($P < 0.05$). The groups presented different ($P < 0.05$) incidence rates of hemodynamically significant patent ductus arteriosus (hsPDA) . Ridit analysis suggested that the premature infants (PIs) with hsPDA, multiple microbial pulmonary infections, or *Klebsiella pneumoniae* pneumonia had more severe illness. **Conclusion:** CHD, hsPDA, MV ≥ seven days, reintubation, pneumonia, especially multiple microbial pulmonary infections, and *Klebsiella pneumoniae* pneumonia are correlated with the severity of BPD and can be used as BPD progression predictor.

Keywords: BPD; Preterm infant; CHD; hsPDA;, Pneumonia; Mechanical ventilation.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication in premature infants (PIs), especially in situations of very or extremely low birth weight (VLBW/ELBW) babies. However, the pathogenesis of BPD is still unclear and involves multiple factors, including genetic susceptibility, intrauterine factors, postnatal shock, mechanical ventilation, oxygen poisoning, pulmonary edema, infection etc. A long-term study monitoring PI lung development found significantly lower FEV1/FVC (First second forced expiratory volume accounts for the percentage of forced vital capacity) in adult BPD patients with a tendency towards airway obstruction compared with individuals without BPD in lung function tests.[1] Infants with BPD also have an increased risk of developing lower respiratory illnesses and allergic respiratory tract diseases in the future.[2] The incidence of congenital heart disease (CHD) in newborns is 5-8/1000,[3] and the incidence is higher in premature infants, especially in children with low gestational age (SGA).[4] CHD with a left-to-right shunt can aggravate pulmonary circulation pressure, and the shear force of the change will damage the vascular endothelium cells (ECs).[5] A series of changes, such as pulmonary inflammation, blood coagulation, oxidative stress, vascular proliferation, and the accumulation of inflammatory cells and fibroblasts, result from the damaged ECs.[6,7] It can increase lung injury and accelerate pulmonary vascular remodeling, eventually leading to pulmonary hypertension (PH). PH is also among the serious complications of BPD.[8,9] Since the relationship between CHD and BPD is still unclear, it is indispensable to identify the risk factors to prevent and treat BPD and meliorate the prognosis of a child patient. This study retrospectively analyzed the clinical data of children with different BPD degrees, followed by their subsequent hospitalization, in addition to exploring the risk factors for BPD severity to provide a basis for the prevention and treatment of BPD.

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METHODS

Study design and participants

We conducted a retrospective study by obtaining the predefined data set from the Guangdong provincial people's Hospital, Guangdong, China. The hospital admitted more than 1300 newborns every year during 2016 to 2020, specifically for this study, we screened the neonates discharged from the hospital between January 2016 and June 2020, in addition to and all related cases included in the 2018 NICHD diagnostic criteria for BPD.

Exclusion criteria:[1] congenital pulmonary dysplasia,[2] genetic metabolic diseases, and[3] chromosome diseases. In this study, infants with BPD were diagnosed and graded according to the criteria modified by the NICHD in 2018,[10] if a premature infant (< 32 weeks' gestational age GA) with BPD had persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks post menstrual age (PMA) required one of the following FiO_2 ranges, oxygen levels, or O_2 concentrations for ≥ three consecutive days to maintain arterial oxygen saturation in the 90-95% range, shown in Table 1 and Figure 1.

According to the BPD grades in the criteria modified by the NICHD in 2018, BPD is classified into the following three levels: grade I – identified as mild in the text, grade II – referenced as moderate, and grades III and IIIA – categorized as severe, according to Table 1.

We extracted the following variables from the electronic medical record system of our hospital: maternal age (years), pre-eclampsia (yes/no), intrauterine infection (yes/no), administration of antenatal steroids (yes/no), gestational age at birth (weeks), birth weight (kg), Apgar score at one minute, sex (male/female), surfactant administration (in/out 30mins after birth), CHD (yes/no), hsPDA (with a ratio of arterial duct diameter to body weight (mm/kg) ≥ 1.4[11]), duration of invasive ventilation (days), reintubation (yes/no), pneumonia (yes/no), septicemia (yes/no), neurological complications (yes/no; including either hypoxic-ischemic brain damage, ventricular hemorrhage, or leukomalacia), retinopathy of prematurity (ROP, yes/no), death before discharge from neonatal care (yes/no), duration of hospitalization (days), family oxygen use (yes/no), weight at discharge (kg), and re-hospitalization (yes/no). CHD included at least one of the following illnesses: patent ductus arteriosus (PDA), ventricular septal defect (VSD), aortic/nonarterial stenosis, valve stenosis/insufficiency, and pulmonary hypertension.

Statistical analysis

Variables of normal distribution were shown as $\chi \pm s$. We applied one-way Analysis of Variance (ANOVA) test to compare the groups. Means and quantiles were used to describe the skewness distribution, while the groups were compared through a rank-sum test. We applied X^2, an independent sample Kruskal-Wallis test, and ridit analysis to compare the enumeration data. Multivariate analysis was performed through unconditional logistic regression analysis. $P < 0.05$ indicates that the difference is statistically significant. Statistical analysis was performed on the SPSS V.23.0 software.

This study used ridit analysis, which can convert the grade data into count data.[12] This algorithm created statistics using 1, 2, 3…, respectively, to represent the different severities of illness: the higher the value the more significant the illness. The mean value of ridit (0.5) is the cut-off point, so it can be concluded that the higher the ridit value the more serious the disease in this group. In this study, the grouping basis of Ridit analysis differed from the Chi-square test. We grouped the cases according to the existence of high-risk events and studied their average case severity. It can directly reflect the direction and degree of influence of risk factors on the disease. $P<0.05$ indicates statistically significant difference.

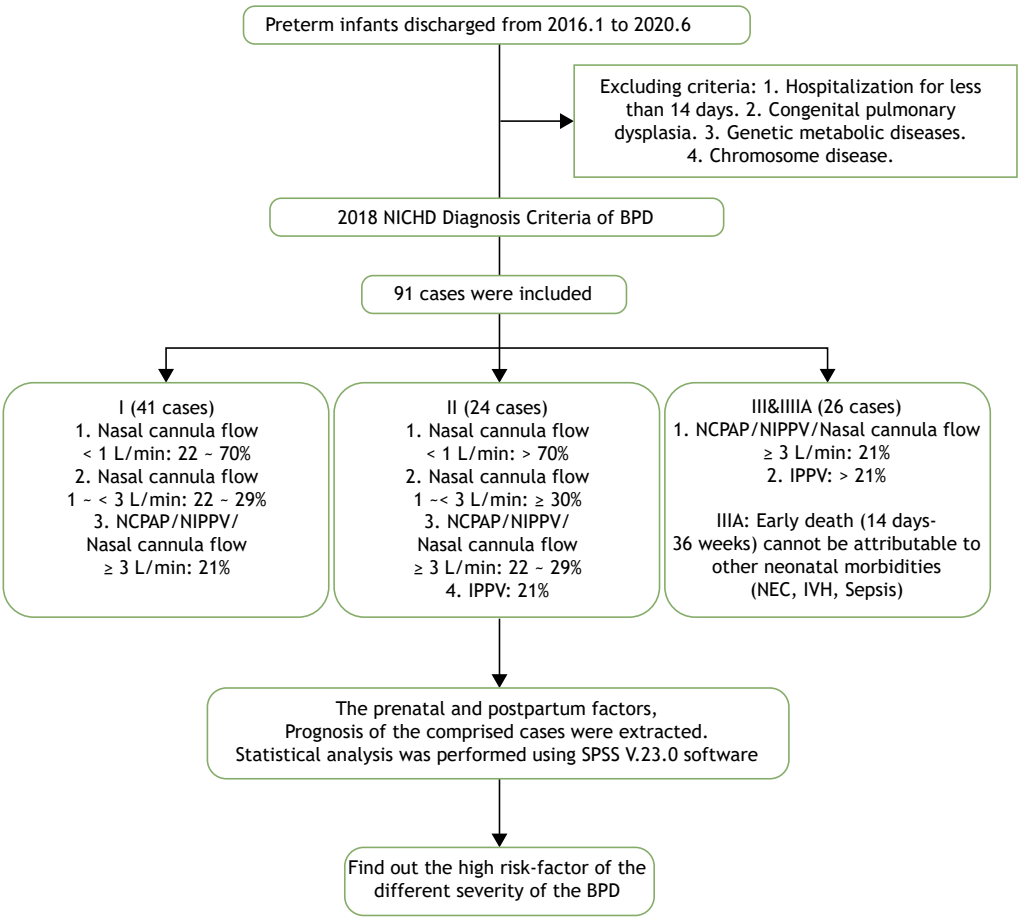
RESULTS

A total of 91 eligible infants participated in this study, including nine deaths. There were 41 cases in grade I BPD, 24 cases in grade II, and 26 cases in grades III and IIIA. Nine of the individuals died, including 1 person in grade I, who developed severe sepsis during

Table 1. BPD grades of the criteria modified by the NICHD in 2018.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min	Nasal cannula flow of 1-<3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	–	21	22-29	22-29	22-70
II	21	22-29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

*Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents. CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; N-CPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation.



* The number following the different modes of pulmonary support reffers to FiO_2

Figure 1. The schematic illustration for the study.

hospitalization; 3 in grade II, with CHD or multiple lung infections; 2 in grade III, with one dying of severe lung infection and the other developing severe NEC, and the remaining 3 in the IIIA. Related complications and genetic diseases were excluded. The minimum and maximum gestational ages (GA) were 25.43 weeks and 31.86 weeks, respectively, with an average of 28.88 ± 1.63 weeks. The participants had a median birth weight of 1.100 kg (0.920-1.290 kg). No significant differences were found in GA, birth weight, sex ratio, or small for gestational age (SGA) ratio among the three groups (P > 0.05), shown in Table 2.

Significant differences appeared in the proportion of CHD and pneumonia among the three groups (PCHD = 0.028, P pneumonia = 0.012, P < 0.05). Further pairwise comparison between groups showed a higher CHD proportion in the severe group than in the moderate one (P = 0.025), while the general difference in the hsPDA proportion among the three groups was significant as well (P = 0.04). The severe group had a higher pneumonia ratio than the mild group (P = 0.006), while the comparison between the other groups was not statistically significant (P > 0.05). This study also conducted a further investigation on the pulmonary infections of the selected children and found statistically significant differences (P = 0.033) in the proportion of *Klebsiella pneumoniae* pneumonia among the groups, while the incidence of multiple microbial pulmonary infections and sepsis among the infants with pneumonia did not show any inter-group differences. The study showed no statistically significant differences in the administration of antenatal steroids, maternal factors (age, pre-eclampsia), low Apgar one minute score (less than or equal to seven), intrauterine infection, or sepsis among the three groups (P > 0.05), as shown in Table 2 and Figure 2.

The three groups showed statistically significant (P = 0.003) proportion of reintubation, with the severe group with the highest value (P < 0.05). There was no significant difference in the number

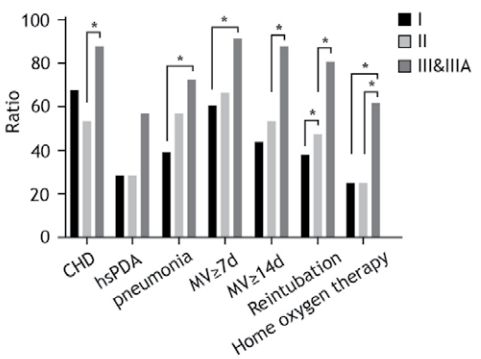
Table 2. Comparison of risk factors, treatment and prognosis of different severity of BPD.

		I N = 41	II N = 24	III/IIIA N = 26	F/X²/Z	P
GA (weeks)		28.8±1.49	28.81±1.55	29.06±1.9	0.217	0.806
Birth weight (kg) M (P25, P75)		1.100 (0.940,1.247)	1.180 (0.942,1.331)	1.070 (0.847,1.385)	1.148	0.563
SGA(%)		4 (9.8)	6 (25)	8 (30.8)	4.987	0.083
Antenatal corticosteroids (%)		18 (48.6)	11 (47.8)	7 (30.4)	2.173	0.337
pre-eclampsia (%)		4 (9.8)	5 (20.8)	3 (11.5)	1.709	0.425
CHD (%)		28 (68.3)	13 (54.2)	23 (88.5)	7.183	0.028
PDA (%)		18 (48.9)	9 (37.5)	17 (65.4)	4.477	0.107
HsPDA(%)		12(29.3)	7(29.1)	15(57.7)	6.428	0.040
Maternal age≥35(%)		12 (35.3)	8 (44.4)	7 (35)	0.494	0.781
Lung infection	Pneumonia(%)	14 (34.1)	14 (58.3)	19 (73.1)	10.239	0.006
	Multiple microbial pulmonary infection (%)	4(28.6)	3(21.4)	11(77.9)	5.334	0.069
	Pneumonia-sepsis (%)	6(42.9)	4(28.6)	3(15.8)	2.51	0.285
	Klebsiella pneumoniae pneumonia (%)	3(21.4)	2(14.3)	10(52.6)	6.802	0.033
Septicemia (%)		17 (41.5)	8 (33.3)	7(26.9)	1.523	0.467
intrauterine infection (%)		10 (24.4)	10 (41.7)	7(26.9)	2.297	0.317
MV≥3d		30 (73.1)	19 (79.2)	25 (96.2)	5.632	0.06
MV≥7d		25 (61.0)	16 (66.7)	24 (92.3)	8.016	0.018
MV≥14d		18 (43.9)	13 (54.2)	23 (88.5)	13.455	0.001
Apgar score at 1 min≤7		22 (59.5)	11 (52.4)	15(65.2)	0.75	0.687
Surfactant administration ≤30min (%)		6 (15.8)	6 (25)	4 (16.7)	0.907	0.638
Reintubation (%)		15 (37.5)	11 (47.8)	18 (81.8)	11.361	0.003
Neurological complications (%)		15 (36.6)	10 (41.7)	10 (38.5)	0.165	0.921
ROP (%)		25 (61)	10 (41.7)	12 (46.2)	2.7	0.259
Home oxygen therapy (%)		10 (25)	5 (25)	13 (61.9)	9.367	0.009
Weight growth (kg/weeks)		0.110±0.033	0.112±0.423	0.120±0.090	0.257	0.774
re-hospitalization (%)		14(35)	4(20)	7(36.8)	1.699	0.428
Death (%)		1 (2.4)	3(12.5)	5(19.2)	5.283	0.071

The deaths and those discontinued treatment were excluded from the readmission analysis.

of patients who had mechanical ventilation (MV) for more than three days among the three groups ($P > 0.05$). Statistically significant difference (P 7d = 0.018, P 14d = 0.001) occurred when invasive ventilation extended from 7 to 14 days. The severe group presented a higher ratio ($P < 0.05$), but no difference was shown between the mild and moderate groups. In addition, there was no significant difference in the number of patients treated with pulmonary surfactant (PS) within 30 minutes after birth among the three groups ($P > 0.05$), as indicated in Table 2 and Figure 2.

The study found a significantly different (P = 0.009) proportion of PIs with different degrees of BPD treated with home oxygen therapy, in addition to



*represents P< 0.05 for comparison between the tow groups.

Figure 2. Pairwise comparison of risk factors and prognosis between groups.

much higher values in the severe groupthan in the mild and moderate groups (P < 0.05). The incidence of neurological complications and ROP, mortality, weight growth rate in NICU and the re-hospitalization rate were not significantly different among the three groups (P > 0.05). The ratio of home oxygen therapy in BPD children with different severities was statistically significant (P = 0.009). Notably, the cases of death and individuals who discontinued treatments were excluded from the readmission analysis, as shown in Table 2 and Figure 2.

Our study also conducted a ridit analysis, which found significantly more serious values of hsPDA-PIs (ridit = 0.619, P < 0.05), as well as no difference between PIs with mild to moderate PDA. The group experiencing recurrent intubation or pneumonia had a more severe condition (ridit > 0.5, P < 0.001). We account for the duration of invasive ventilation and performed a ridit analysis considering whether the MV duration was longer than seven or 14 days. The result showed that more than seven days of invasive ventilation could aggravate the BPD (ridit > 0.5 P < 0.001). The following three factors were analyzed in pneumonia-PIs enrolled in the study. The condition of BPD-PIs with multiple pulmonary infections is more serious than single pathogen infection (ridit = 0.654,P < 0.05) and BPD-pneumonia-PIs with *Klebsiella pneumoniae* infection is more severe than infection with other pathogens (ridit = 0.678, P < 0.05). The presence of sepsis did not affect the severity of BPD-pneumonia-PIs (P > 0.05), as indicated in Table 3.

BPD severity was the dependent variable and the factors of MV ≥ seven days, pneumonia, reintubation and CHD were included in multiple regression analyses. The model proved significant (P = 0.001). R^2 was 0.262, which means that the model could explain a 26.2% variation in BPD severity. The results suggested that pneumonia and reintubation were the risk factors for BPD progression from mild to moderate. P pneumonia = 0.025, OD = 3.769, 95% CI(1.181,12.027);P reintubation = 0.037, OD = 4.71, 95% CI(1.098,20.211). In addition, the CHD was significantly associated with severe BPD. P CHD = 0.025, OD = 5.267, 95% CI(1.177,23.557), as shown in Table 4.

DISCUSSION

Currently, SGA is widely believed to be a risk factor related to BPD severity. In recent years, most NICUs in China have adopted the Fenton 2013 or INTERGROWTH-21st standards to define newborns' growth. However, detecting SGAs always differs due to racial variations. Therefore, in this study, we divided the included cases according to the curves released by Capital Children's Research Institute in 2020 of neonatal weight at different GAs in China.[13] The results were contradictory to the dominant opinion. This curve could reflect GAs distribution and birth weight of PIs with BPD in China more accurately. Although a statistical error due to insufficient samples should not be ruled out, the result was likely to reflect a trend of disease characteristics related to lower birth

Table3. The RIDIT analysis for the high risk factors of different severity of BPD.

Factors	Average Ridit	T	P
Pneumonia	0.680	4.773	<0.001
Reintubation	0.698	4.973	<0.001
MV≥7d	0.663	4.485	<0.001
MV≥14d	0.698	5.078	<0.001
Mild to Moderate PDA	0.457	-0.468	0.651
HsPDA	0.619	2.335	0.026
Multiple microbial pulmonary infection	0.654	2.243	0.039
Pneumonia-sepsis	0.348	-2.061	0.062
Klebsiella pneumoniae pneumonia	0.678	2.417	0.030

Multiple microbial pulmonary infection, Pneumonia-sepsis, Klebsiella pneumoniae pneumonia were analyzed among the pneumonia-PIs enrolled in the study.

Table 4. Multivariate logistic-regression analysis of risk factors for different severity of BPD.

Severity of BPD	Risk factors	P	OD	Exp(B) 95% CI	
I-II	CHD	9.277	2.321	9.509	10.581
	Reintubation	0.037	4.710	1.098	20.211
	Pneumonia	0.025	3.769	1.181	12.027
	MV≥7d	0.443	2.086	0.319	13.643
	constant	0.021			
II-III(A)	CHD	0.030	5.267	1.177	23.557
	Reintubation	0.177	3.033	0.607	15.159
	Pneumonia	0.666	1.334	0.360	4.940
	MV≥7d	0.413	2.321	0.309	17.411
	constant	0.016			

CHD, congenital heart disease; MV, mechanical ventilation.

weight in a moment where prenatal steroid treatment is becoming more sophisticated.

CHD is associated with increased mortality of premature infants and incidence of some diseases, including ventricular hemorrhage, pulmonary hemorrhage, necrotizing enterocolitis etc.[14] We statistically analyzed the incidence of CHD among the participating cases. CHD turned out to have been significantly associated with severe BPD (OD = 5.267, P = 0.03). However, Pappas et al.[15] reported no relationship between CHD and BPD in infants with a VLBW of less than 1000g. There was still much debate about the relationship between CHD and BPD. Newborns with CHD have impaired cardiac function and required extensive respiratory support after surgery, in addition to being often diagnosed with BPD at the time of discharge. It is the reason why the effect of CHD on BPD has been consistently underestimated.

In this study, the incidence of hsPDA in enrolled cases was also statistically analyzed. The ridit analysis revealed that the condition of PIs with hsPDA was significantly more serious (ridit = 0.619, P < 0.05), no difference appeared between mild to moderate PDA and healthy children. Changes in hemodynamics caused by these specific heart malformations were likely to be the leading cause of BPD exacerbation. In the past, the blood shunt caused by atrial septal defect (ASD) was considered harmless in pediatrics, but it was only suitable to infants with well-developed lungs, a theory that disregarded the size of the ASD. Lung development in PIs, especially extremely premature infants, is already imperfect. For infants with lung injury, any factor leading to increased pulmonary circulation burden aggravates the condition.[16]

Compared with full-term infants, preterm infants with GA <32w have higher blood pressure in adolescence, while the left ventricle and aorta shrink.[17] Whether their lungs were over circulated or not, infants with CHD would have impaired pulmonary vascular development and alveolar II cell secretion of pulmonary surfactant to a certain extent. Therefore, while studying the PIs with CHD, the influence of hemodynamics deserves more attention. Different types of heart malformations should be analyzed according to the condition of the disease to obtain more accurate results and provide a reference for clinical diagnosis and treatment. Recently, in a follow-up study of almost 100 children with allergic respiratory diseases, our team found that CHD-children had high airway reactivity after surgery, in addition, asthma incidence was higher than in healthy children.

Prolonged use of invasive ventilation can cause severe lung damage and affect newborns' development throughout life. Studies have shown increased risk of BPD in PIs with a GA less than 28 who had an MV duration longer than three to five days.[18] When investigating 200 infants, Amit Sharma concluded that along with the diagnostic criteria established in 2001, the cumulative MV for ≥ seven days in the first 21 days after birth predicted moderate to severe BPD.[19] Although early extubation is the most direct manner to alleviate lung injury caused by MV,[20] it often fails due to improper timing. Reintubation is a significant risk factor for BPD.[21] In this study, the further ridit and regression analyses performed revealed that those who experienced reintubation represented more serious cases. Considering that tn recent years, the characteristics of BPD have changed, to redetermine the impact of invasive ventilation duration on BPD-PIs and explore better timing for extubation, our analyses followed the new diagnostic criteria in 2018. Our results suggested that BPD-PIs with MV ≥ seven days were more serious, but proved insignificant in multiple logistic regression analysis. The final diagnosis of moderate and severe BPD in individuals with reintubation was about five times as likely as mild BPD (OD = 4.71), suggesting that it is questionable whether to shorten the duration of invasive ventilation as much as possible.

Ventilator-associated pneumonia (VAP) is one of the critical factors leading to prolonged respiratory support in neonates and a risk factor for BPD in PIs.[22] On this basis, this study concluded that pneumonia was also associated with the severity of BPD (OD = 3.769), which was a significant factor aggravating the diseases. We further analyzed the pulmonary infection of different BPD-PIs severity. The cases of babies with multiple pulmonary infections and *Klebsiella pneumoniae* pneumonia were more serious than those with a single pathogen or non-*Klebsiella pneumoniae* infection (ridit > 0.5, P < 0.05). Such result was likely related to severe BPD, but the chance of lung infection (multiple pathogens/common hospital pathogens) caused by the prolonged respiratory support should not be ruled out. In addition, due to the insufficient number of cases or the high vigilance of our center for sepsis, the influence of pneumonia combined with sepsis on the condition of BPD was insignificant. High neutrophil-to-lymphocyte ratio at 72 hours has been reported as an early predictor of BPD.[23] Therefore, for a better knowledge on the relationship between pneumonia and BPD, the infection time should be considered.

Respiratory support and nursing care after extubation also play a decisive role in extubation outcomes. Safer alternatives are urgently needed to reduce the lung damage caused by prolonged MV. Comparing with CPAP, noninvasive mechanical ventilation (NIMV) reduced the failure rate of extubation[24]and reduced the incidence of BPD. Heated-Humidified High Flow Nasal Cannula (HFNV) can also minimize re-intubation and accelerate CO2 removal.[25-28]

BPD has a long-term influence on respiratory growth. A statistical analysis of extremely premature infants between 2016 and 2018 conducted in the UK found that 68% of the PIs who still needed home oxygen therapy after discharge, had BPD,[29] while 49% needed another hospitalization within one year after birth.[30,31] Our study analyzed the prognosis of the comprised infants and found a positive correlation of the probability of discharge with oxygen and BPD

severity. Simultaneously, there was no difference in the incidence of neurological complications, ROP, and re-hospitalization among babies with different severities. Consistent with the results of previous studies, the three groups showed little difference in the rate of weight gain during hospitalization, possibly due to the comprehensive and continuous monitoring of the infants' development and health in the hospital.[32] A more detailed and lasting follow-up plan is required for a further understanding on the long-term effects of BPD on children's development, such as cognition, language, and lung development.

In this study, ridit analysis was introduced to convert grade data into measurement data, which could intuitively reflect the influence direction and degree of different disease factors. However, it could not avoid the reliance on medical record information, selection bias, or the absence of unmeasured variables in the retrospective study. Data bias was attenuated by clear inclusion and exclusion criteria and detailed perinatal and postpartum cohort study designs.

In conclusion, CHD, hsPDA, MV ≥ seven days, reintubation, pneumonia, especially the multiple microbial pulmonary infections, and *Klebsiella pneumoniae* pneumonia are significantly associated with BPD severity of and can be regarded as predictive events for moderate and severe BPD. The probability of home oxygen therapy is positively correlated with the condition of BPD. The specific effect of CHD on the long-term lung development of children with BPD will be our team's primary direction.

AUTHOR CONTRIBUTIONS

Contribution statement: (I) Conception and design: Minqiao Jian, Shaoru He; (II) Administrative support: Yumei Liu; (III) Provision of study materials or patients: Bowen Feng, Juan Gui, Manli Zheng; (IV) Collection and assembly of data: Minqiao Jian, Caisheng Liu,Xiaohui Zhang; (V) Data analysis and interpretation: Minqiao Jian, Xiaoqing Liu, Manli Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All author.

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ORIGINAL ARTICLE

Risk factors for recurrent wheezing in preterm infants who received prophylaxis with palivizumab

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ABSTRACT

Objective: To determine the prevalence of recurrent wheezing (RW) in preterm infants who received prophylaxis against severe infection with respiratory syncytial virus (RSV) and to identify genetic susceptibility (atopy or asthma) and risk factors for RW. **Methods:** This was a cross-sectional study involving preterm infants who received prophylaxis with palivizumab at a referral center in Brazil during the first two years of age. A structured questionnaire was administered in a face-to-face interview with parents or legal guardians. **Results:** The study included 410 preterm infants (median age = 9 months [0-24 months]). In the sample as a whole, 111 children (27.1%; [95% CI, 22.9-31.5]) had RW. The univariate analysis between the groups with and without RW showed no differences regarding the following variables: sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding, number of children in the household, day care center attendance, pets in the household, and smoking caregiver. The prevalence of RW was twice as high among children with bronchopulmonary dysplasia (adjusted OR = 2.08; 95% CI, 1.11-3.89; p = 0.022) and almost five times as high among those with a personal/family history of atopy (adjusted OR = 4.96; 95% CI, 2.62-9.39; p < 0.001) as among those without these conditions. **Conclusions:** Preterm infants who received prophylaxis with palivizumab but have a personal/family history of atopy or bronchopulmonary dysplasia are more likely to have RW than do those without these conditions.

Keywords: Infant, premature; Respiratory sounds; Asthma; Palivizumab; respiratory syncytial viruses; Respiratory hypersensitivity.

INTRODUCTION

Children up to three years of age are subject to several diseases that are manifested by wheezing.[1] Approximately 45% of infants have one episode of wheezing in their first year of life, and about 20% have recurrent wheezing (RW).[1] This condition can decrease their quality of life and increase the demand for health care services and consequent hospitalizations due to the high prevalence of severe wheezing episodes.[2]

Preterm newborns, especially extremely premature infants, are more likely to have chronic lung diseases.[3-5] The structural damage to the lungs of infants caused by pregnancy-related events, such as intrauterine growth restriction, chorioamnionitis, and neonatal diseases, leads to impaired lung function.[6] A systematic review published in 2014 showed that prematurity is related to an increased risk of RW, especially in the group of infants born at fewer than 32 weeks of gestational age.[7] A cross-sectional study with 445 children evaluated the risk factors associated with RW in preterm infants.[8] Birth weight < 1,000 g, < 28 weeks of gestational age, personal or family history of atopy, and two or more children living in the same household were considered risk factors for RW.[8]

Up to two years of age, due to the immaturity of the immune system and modulation of innate and adaptive responses, children are more prone to the action of infectious agents.[9] Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in breastfed young children[10-13] and is responsible for approximately 60 million respiratory infections per year worldwide.[14-16] Exposure to RSV occurs in 60-70% of

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infants during their first year of life.[11] It is estimated that almost all children have already been infected with RSV by the age of two,[17] and approximately 40% will present with LRTI symptoms due to the initial infection. [18] The risk of severe respiratory disease caused by this pathogen is related both to the immunological characteristics of the host and to the viral ability to cause damage.[17,18]

Severe RSV infection in the first two years of life has been associated with long-term respiratory morbidity, decreased pulmonary function, RW, and asthma.[19] Blanken et al.[20] showed that hospitalization caused by viral infection of the lower respiratory tract is a determining factor for RW in healthy preterm children.

Carbonell-Estrany et al.[21] evaluated the impact of hospitalization due to RSV infection on the health of six-year-old children who had been preterm infants (32-35 weeks of gestational age) and confirmed an increased risk of asthma after severe RSV infection in childhood. However, other authors have shown that there is no well-established association between RSV infection and asthma in healthy preterm infants.[22,23] In a study involving preterm children who received prophylaxis with palivizumab and were monitored until they reached six years of age, the authors concluded that immunoprophylaxis had no impact on asthma prevention, but there was a reduction in the RW rate.[24] However, Simões et al.[25] found that the use of passive immunization decreased the risk of RW only in children without a family history of atopy, which suggests that RSV predisposes to RW regardless of atopy.[26] Simões et al.[8] evaluated risk factors associated with RW in preterm children with a high probability of severe RSV infection. In that study, the authors concluded that low gestational age and presence of atopy were the major risk factors associated with RW.[8]

In 2020, a review by experts convened by the World Health Organization showed that a causal association of RSV-related LRTI with RW and asthma was inconclusive.[27] It is not yet clear whether severe RSV infection during the first year of life alters the immune response and triggers the onset of RW or whether it is simply a marker of genetic predisposition to RW.[28] Therefore, the present study is justified, because risk factors associated with RW can be evaluated despite the possible bias of RSV infection in the population of preterm infants who received immunoprophylaxis against RSV.

The aims of the present study were to determine the prevalence of RW in preterm infants who received prophylaxis with palivizumab against severe RSV infection and to identify genetic susceptibility (atopy/asthma) and risk factors for RW.

METHODS

This was a cross-sectional study based on interviews with parents or legal guardians of preterm infants who received passive immunization (palivizumab) against RSV at the *Centro de Referência para Imunobiológicos Especiais* (Referral Center for Special Immunobiologics) at the State University at Campinas, Brazil. Patient selection and interviews took place in two different years (2012 and 2016) in order to increase the convenience cohort size. The same individuals interviewed the participants using the same questionnaire in both years in order to avoid measurement bias. All preterm infants with gestational age < 36 weeks were included. Full-term newborns and infants diagnosed with heart disease, pulmonary malformation, or pulmonary hypertension were excluded.

RW was defined as three or more wheezing attacks during a one-year-period, either in the first year of life or in the year prior to the interview. Asthma is a disease with several phenotypes and can present with respiratory signs and symptoms, including wheezing. Many children have RW, but this is not always indicative of asthma.[27] In our study, children with RW were considered atopic if they had a history of atopic dermatitis, a medical diagnosis of asthma, or a father or mother with a history of asthma.

A structured questionnaire was used, based on a reduced version of the International Study of Wheezing in Infants questionnaire,[29] which was developed to standardize the investigation of RW. That questionnaire is a tool that provides information on the frequency of RW in childhood, as well as on the treatment and risk factors associated with the condition. The questionnaire was administered to the parents or legal guardians at the referral center.

All statistical analyses were performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). We determined the prevalence of RW (95% CI). In order to evaluate the association of RW with selected variables (sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding duration, day care center attendance, maternal smoking during pregnancy, smoking caregiver, pets in the household, number of children in the household, presence of bronchopulmonary dysplasia, and presence of atopy), we used ORs, initially determined by univariate logistic regression and, subsequently, in an adjusted manner, by unconditional multivariate logistic regression using the Wald method (forward stepwise technique). The probability of inclusion in the model was 0.05, and the probability of exclusion from the model was 0.10. All predictor variables with $p \leq 0.05$ in the univariate analysis and those considered as potential confounding factors (i.e., $0.05 < p < 0.20$) were selected for inclusion in the multivariate model.

The present research project was approved by the Research Ethics Committee of the State University at Campinas (#142,928/2012 and #1,030,707/2015). All parents or legal guardians signed the written informed consent form.

RESULTS

We interviewed parents or legal guardians of 745 patients who received palivizumab. Preterm patients

with gestational age < 36 weeks were selected for the study. Of the 745 individuals interviewed, 57 declined to participate. In addition, 265 and 13 of the infants had heart disease and pulmonary malformation or pulmonary hypertension, respectively, and were excluded. Therefore, 410 preterm children who received palivizumab were included in the study (Figure 1).

The children were classified as having RW (three or more episodes of wheezing in 1 year) or as not having RW. Data on the presence of atopy and the gestational age were collected. Table 1 shows the demographic and clinical characteristics of the sample.

The overall prevalence of RW was 27.1% (95% CI, 22.9-31.5). Table 2 shows the prevalence of RW in relation to independent variables. The univariate logistic regression analysis showed no differences regarding the following variables: sex, ethnicity, maternal level of education, gestational age, birth weight, breastfeeding duration, number of children in the household, day care center attendance, pets in the household, and smoking caregiver.

The chance of developing RW was higher among children whose mothers reported having smoked during pregnancy than among those whose mothers did not (OR = 2.54; 95% CI, 1.06-6.09; p = 0.037; Table 2). Children with a personal history of allergy or whose parents (one or both) had a history of atopy were almost six times more likely to have RW (OR = 5.79; 95% CI, 3.59-9.35; p < 0.001), whereas those diagnosed with bronchopulmonary dysplasia were twice more likely to have RW (OR = 2.10; 95% CI, 1.34-3.29; p = 0.001; Table 2).

For the unconditional multivariate logistic regression analysis, we selected the following variables: atopy, maternal smoking during pregnancy, and bronchopulmonary dysplasia. Sex, number of children in the household, and day care center attendance were considered confounding variables (i.e., 0.05 < p < 0.20). After the analysis, only atopy (p < 0.001) and bronchopulmonary dysplasia (p = 0.022) remained in the model (Table 3). The prevalence of RW was twice as high among children with bronchopulmonary dysplasia (adjusted OR = 2.08; 95% CI, 1.11-3.89; p = 0.022) and almost five times as high among those with a personal/family history of atopy (adjusted OR = 4.96; 95% CI, 2.62-9.39; p < 0.001) as among those without these conditions (Table 3).

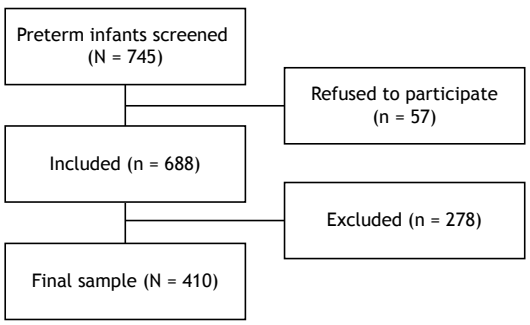

Figure 1. Flow chart of the participant selection process.

DISCUSSION

There are several risk factors reported in the literature associated with RW in the pediatric age group. The prevalence of RW was 27.1% in preterm infants who received palivizumab in the present study. In our sample, the chance of RW was five times higher in the presence of family or personal history of atopy. Although it is well established that there is an association between RSV-related LRTI and RW, it is still unclear whether this association is causal.[30] Several risk factors are related to RW, one of those being atopy.[23]

Simões et al.[25] reported that preventing RSV infection with the use of palivizumab in premature infants without a history of atopy appears to decrease by 80% the relative risk of RW in children from 2 to 5 years of age, an effect that is not seen in those with a history of atopy. In a Brazilian study,[8] atopy and low gestational age were risk factors for RW, and the authors concluded that prophylaxis with palivizumab against RSV significantly reduced the relative risk of subsequent RW in nonatopic premature infants. A systematic review showed that a family history of asthma or atopy is important in the association between severe RSV infection and RW.[23] The authors also suggested that the data in the literature do not support the hypothesis of a causal link between RSV-related LRTI and subsequent wheezing.[23] Another finding of that review was that there was no evidence that immunoprophylaxis protects against subsequent wheezing illness.[23]

Table 1. Demographic and clinical characteristics of the patients studied (N = 410).

Characteristic	n	%
Male	194	47.3
Ethnicity		
Non-White	103	25.1
White	277	67.5
Maternal level of education		
Middle school	65	15.8
High school	146	35.6
Higher education	183	44.6
Recurrent wheezing	111	27.1
Hospitalizations due to wheezing	74	18
Hospitalizations due to pneumonia	60	14.6
Use of inhaled corticosteroid	182	44.4
Atopy	113	27.5
Characteristic	**Median**	**Min-max**
Gestational age, weeks	28	23-36
Birth weight, grams	1.028	505-2.575
Breastfeeding, months	3	0-29
Age at first wheezing attack, months	4	0[a]-17

Min-max: minimum-maximum values. [a]Age < 30 days of life.

Table 2. Risk factors for recurrent wheezing based on the reduced version of the International Study of Wheezing in Infants questionnaire.[29]

Variable	Wheezing				Total	p*	OR	95% CI
	Yes		No					
	n	%	n	%				
Sex								
Male	60	30.9	134	69.1	194	0.097	1.45	0.94-2.24
Female	51	23.6	165	76.4	216		1.00	
Ethnicity								
Non-White	29	28.2	74	71.8	103	0.889	1.04	0.63-1.72
White	76	27.4	201	72.6	277		1.00	
Maternal level of education								
Middle school	13	20.0	52	80.0	65	0.280	0.68	0.34-1.36
High school	44	30.1	102	69.9	146	0.501	1.18	0.73-1.91
Higher education	49	26.8	134	73.2	183		1.00	
Gestational age, weeks								
23-26	33	30.6	75	69.4	108	0.812	1.14	0.38-3.47
27-29	51	25.4	150	74.6	201	0.823	0.88	0.30-2.60
30-32	20	28.6	50	71.4	70	0.947	1.04	0.33-3.30
33-36	5	27.8	13	72.2	18		1.00	
Birth weight, g								
< 1,000	57	29.8	134	70.2	191	0.645	0.71	0.16-3.07
> 1,000-1,500	40	23.5	130	76.5	170	0.375	0.51	0.12-2.24
> 1,500-2,000	8	25.0	24	75.0	32	0.482	0.56	0.11-2.86
> 2,000	3	37.5	5	62.5	8		1.00	
Breastfeeding, months								
Not breastfed	17	27.9	44	72.1	61	0.904	1.06	0.40-2.84
1-3	16	17.6	75	82.4	91	0.283	0.59	0.22-1.55
4-6	12	19.4	50	80.6	62	0.427	0.66	0.24-1.84
≥ 7	8	26.7	22	73.3	30		1.00	
Children in the household								
3-4	14	23	47	77.0	61	0.415	1.42	0.61-3.31
2	12	41.4	17	58.6	29	0.012	3.37	1.30-8.71
1	23	24.7	70	75.3	93	0.247	1.57	0.73-3.36
None	13	17.3	62	82.7	75			
Day care center attendance								
Yes	13	37.1	22	62.9	35	0.104	1.83	0.88-3.80
No	82	24.4	254	75.6	336		1.00	
Pets in the household								
Yes	46	27.2	123	72.8	169	0.533	1.16	0.73-1.85
No	49	24.4	152	75.6	201		1.00	
Maternal smoking during pregnancy								
Yes	10	45.5	12	54.5	22	0.037	2.54	1.06-6.09
No	84	24.7	256	75.3	340		1.00	
Smoking caregiver								
Yes	7	18.4	31	81.6	38	0.289	0.63	0.27-1.48
No	84	26.8	234	73.6	318		1.00	
Atopy								
Yes	61	54.0	52	46.0	113	< 0.001	5.79	3.59-9.35
No	50	16.8	247	83.2	297		1.00	
Bronchopulmonary dysplasia								
Yes	71	34.1	137	65.9	208	= 0.001	2.10	1.34-3.29
No	40	19.8	162	80.2	202		1.00	

*Wald test.

Bronchopulmonary dysplasia is a risk factor for severe RSV infection, but its association with RW in infants is unclear.[31,32] Preterm patients who received immunoprophylaxis and were diagnosed with

Table 3. Multivariate logistic regression for factors associated with recurrent wheezing.

Factor	Wheezing				Total	p	Adjusted OR	95% CI
	Yes		No					
	n	%	n	%				
Bronchopulmonary dysplasia								
Yes	71	34.1	137	65.9	208	0.022	2.08	1.11-3.89
No	40	19.8	162	80.2	202		1.00	
Atopy								
Yes	61	54.0	52	46.0	113	< 0.001	4.96	2.62-9.39
No	50	16.8	247	83.2	297		1.00	

*Wald test.

bronchopulmonary dysplasia were twice more likely to have RW when compared with those who were not. The literature shows that children with severe bronchopulmonary dysplasia at 6 months of age will more commonly present with respiratory symptoms than will those with mild or moderate bronchopulmonary dysplasia.[31,32] However, other risk factors should be investigated as markers of future onset of respiratory symptoms.[31]

We concluded that maternal smoking during pregnancy is a risk factor for RW. However, this factor was eliminated in the unconditional multivariate logistic regression analysis. Our conclusion was corroborated by a meta-analysis that evaluated seven articles, involving a total of 8,579 infant cases of RW, regarding the association between maternal smoking during pregnancy and the risk of RW in childhood.[33] The authors concluded that maternal smoking during pregnancy could increase the risk of RW in childhood.[33] However, that association was found only in the cross-sectional studies evaluated, but not in the cohort studies.[33] In addition, the authors considered that the maintenance of maternal smoking during the postnatal period was a confounding factor and emphasized the need for further studies with a cohort design in order to elucidate this issue better.[33]

On the basis of our study group results, family atopy and bronchopulmonary dysplasia were risk factors for RW. Simões et al.[8] demonstrated an increased chance of RW in preterm infants with a personal history of food allergy or atopic dermatitis. A review article that evaluated the relationship between severe RSV infection and subsequent asthma concluded that there is a high probability that environmental factors, such as RSV infection, act as triggering events.[34] Therefore, we highlight the importance of immunoprophylaxis to prevent preterm infants from having severe RSV infection.

Memory bias can be considered a limitation of the present study, given the importance of the exact number of wheezing episodes for classifying the patient as a recurrent wheezer, and the fact that this information was obtained from parents or legal guardians rather than from medical reports. Another limitation is that there was no control group, because it would be unethical to deprive preterm children of the immunoprophylaxis program in accordance with the criteria defined by health care authorities.[35] Data collected in two nonconsecutive years might have introduced a patient selection bias. However, there were no changes in the palivizumab prophylaxis protocol (gestational age, association with pulmonary disease, and heart disease), and the population treated at our center was the same in terms of socioeconomic characteristics.

In conclusion, RW has different phenotypes, and the risk factors involved are yet to be fully understood. In the present study, the use of immunoprophylaxis against RSV infection did not prevent 27,1% of infants from having RW. Thus, genetic factors related to atopy might play an important role as a predictive factor of RW. Other cohort studies are needed to improve the elucidation of the cause-effect relationship between RSV infection and RW.

AUTHOR CONTRIBUTIONS

MBM and AADCT: conception and design of the study; data acquisition and interpretation; drafting the article; critical review of the relevant intellectual content; and approval of the final version. NYM, LG, MSO, MRVC, GLMTR, EOM, MAGOR, and JDR: data acquisition; critical review of relevant intellectual content; and approval of the final version. AMM: Data acquisition, analysis, and interpretation; critical review of relevant intellectual content; and approval of the final version.

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ORIGINAL ARTICLE

Socio-demographic and psychological features associated with smoking in pregnancy

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ABSTRACT

Objective: To investigate how social and psychological characteristics differ between pregnant women who smoke and do not smoke. To explore associations between social and psychological features with changes of smoking habits by the end of pregnancy. **Methods:** A case-control study was set up. Smokers cases were never-smokers and ex-smokers controls. Pregnant women (n=328) from public prenatal services were interviewed. Socio-demographic data and psychological variables – personality traits, anxiety, depression, perceived stress, maternal fetal-attachment - were measured. Saliva samples were collected to measure cotinine and to check self-informed smoking status. In addition, 66 smokers were also assessed regarding smoking habits by late pregnancy. Smoking status was defined as a dependent variable. Exposure factors were analyzed through odds ratios. Logistic models and contingency tables were employed according to the nature of variables. "Qualitative change in smoking" was defined as a dependent variable for the last evaluation, and a logistic regression model was built. **Results:** Lower schooling, higher age, use of alcohol and drugs, living without a partner, and passive smoking showed associations with smoking. Anxiety, depression and perceived stress also exhibited positive association with smoking. Among personality traits, only Neuroticism was associated with smoking. None of the variables were associated with qualitative change in smoking by the end of pregnancy. **Conclusion:** Smoking during pregnancy is associated with more unfavorable social conditions. Pregnant women who smoke exhibit more negative psychological states than nonsmokers, including a profile of accentuated Neuroticism. None of the investigated variables could predict changes in smoking during pregnancy.

Keywords: Smoking; Pregnancy; Psychology; Psychosocial factors; Personality traits; Big five factor model of personality; Perceived stress; Anxiety; Depression.

INTRODUCTION

Smoking in pregnancy is a serious health issue, since both mother and fetus are subject to toxic substances of cigarettes.[1] Smoking during pregnancy has been associated, among others, with placenta *previa*, spontaneous abortions, preterm delivery, low birth weight, and high fetal mortality.[2] In addition, several morbid conditions have been described in children of pregnant smokers, even years after delivery.

Regardless of the increasing knowledge about its harms, cigarette use during pregnancy still is a common behavior in several regions of the world. A systematic review, performed with data from more than 100 countries, found that, worldwide, 52.9% of women who smoked daily continued to do it during pregnancy.[3] Though, it is important to recognize that many pregnant women voluntarily quit, with reported rates ranging from 4% to 70%.[4]

Smoking during pregnancy has been associated with several socio-demographic features including mother`s age, poor educational level, and low economic class.[5-7] It has also been associated with some psychological characteristics, including high levels of anxiety, depression, and perceived stress.[8-10] On the other hand, quitting has been associated mainly with higher educational levels, planned gestation, first pregnancy, non-smoking partners, and lower levels of anxiety.[11-13]

Due to the widespread knowledge about the harms of tobacco, pregnant women frequently do not provide trustful information regarding their smoking habits.[1] Studies on smoking during pregnancy have reported disagreements of 28% to 50%, between self-reports and

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cotinine tests.[14] Nevertheless, most studies on socio-demographic and psychological features of pregnant women who smoke lack biological assessments, which may have adversely influenced the results.

The overall prevalence of smoking in Brazil has progressively decreased along the past decades, but the proportion of Brazilian pregnant women who smoke still is estimated to be 14.7%.[3] Despite the relevance of the matter and several studies published in the field, to the best of our knowledge, there is not a published manuscript specifically designed to explore psychological features associated with smoking in Brazilian pregnant women.[15-20]

The objective of the present study was to compare socio-demographic and psychological features among Brazilian pregnant women classified as smokers and non-smokers, whose smoking status had been confirmed by biochemical tests. In addition, it was also explored if any of these features could be associated with quitting or reducing smoking at the end of the pregnancy.

METHODS

A case-control investigation was conducted, where pregnant smokers were the case group and pregnant non-smokers the control group. All women completed a first assessment, not later than a gestational age of 24 weeks. In addition, smokers also completed a second assessment around delivery.

A convenience sample of pregnant women attending prenatal care at six public health units in the city of Ribeirão Preto, Brazil, were sequentially invited to participate in the study from July, 2015 through October, 2018.

All women were at least 18 years old, with gestational less than 24 weeks ages. They were classified according to self-reported smoking status in: (i) regular smokers: women who smoked more than 100 cigarettes in lifetime, and at least one cigarette a day in the past six months; (ii) former smokers: women who smoked at least 100 cigarettes in lifetime, but did not smoke any in the past six months, and (iii) never smokers: women who smoked less than 100 cigarettes in lifetime, and did not smoke any in the past six months. Regular smokers were included in a smoker group (SG), while never smokers and former smokers were combined in a non-smoker group (NSG).

Women who reported occasional smoking only, or who had started or stopped smoking in the past six months, were not included. Additional exclusion criteria were illiteracy, use of psychiatric medications, severe co-morbidities, and self-reported smoking status discordant of salivary cotinine measurements. Women who reported use of psychiatric medications and severe comorbidities were excluded due to the potential influence of these factors on smoking related psychological outcomes. Therefore, this exclusion criteria was proposed to control possible biased outcomes.

Women of the SG gave information about their smoking history, including number of cigarettes smoked a day, years of smoking, and answered the Brazilian version of the Fagerström Test of Nicotine Dependence (FTND).[21] Information about smoking habits was also obtained a second occasion, just before or a few weeks after delivering.

Aiming at verifying self-reported smoking status, saliva samples were collected of all volunteers for cotinine measurements, at conclusion of the first evaluation. The employed methodology involved liquid-liquid extraction and gas chromatography for the quantification of nicotine and cotinine. The detection limit of this method is 10ng/ml for nicotine and 6 ng/ml for cotinine.[22] Participants whose smoking status was discordant through biochemical assessment were excluded.

First assessment

All women were interviewed by the same researcher (ATLF), who employed an instrument covering the items: (i) socio-demographic variables, including economic status evaluated by the Brazilian Economic Classification Criteria, which ranges from A (highest) to D/E (lowest), and number of complete years of schooling; (ii) clinical variables related with pregnancy, such as number of gestations and abortions; (iii) pregnancy intention; (iv) anxiety and depression, using the Brazilian version of the Hospital Anxiety and Depression Scale; (v) perceived stress, measured by the Brazilian version of the 10 points Perceived Stress Scale; (vi) use of alcohol and illicit drugs; (vii) exposure to passive smoking in the workplace and at home; (viii) maternal fetal-attachment, and (ix) personality traits, evaluated by the Personality Markers Scale that assess personality according to the Big Five Personality theory.[23-26]

All women, regardless of their smoking status, received an educational leaflet about the hazards of smoking in pregnancy, at the end of the first interview.

Second assessment

The women who composed the SG were interviewed for a second time regarding smoking behavior. Such assessment was conducted near delivery, approximately 36 weeks of the gestation period. The women who could not be interviewed at that time were contacted after delivery. The reached women were asked about current smoking and the number of cigarettes smoked a day.

This study was approved by the Institutional Ethics Committee, and all volunteers signed informed consents before answering the questions and provide saliva samples.

Data Analysis

The two groups created a binary response variable of retrospective causal origin. Smoking status was defined as a dependent variable. Exposure factors were analyzed by odds ratio (OR) measurements, according to the type of independent variable: quantitative analysis

were performed by logistic models, while categorized variables were analyzed by contingency tables.

Exploratory analyses were performed involving independent variables, in order to identify possible sources of bias. Exposure factor analyses were performed with univariate models. Adjusted analyses were done employing Mantel-Haenzel OR calculations for psychological variables in relation to outcome, according to results of exploratory analysis.

An univariate logistic regression model was employed to investigate potential influences of variables identified in the first interview, on changes in smoking habits at the end of pregnancy. A binary variable of qualitative changes was assumed at this time: quitting or decrease versus stability or increase of the number of cigarettes smoked a day.

In order to explore possible biases on associations involving psychological factors, an adjusted analysis involving the variables anxiety, depression, perceived stress, maternal-fetal attachment and the five personality factors was performed. Independent measures that showed significant correlations with these variables in the preliminary exploratory analysis were selected.

RESULTS

A total of 328 volunteers were initially interviewed. Fifty-nine of these subjects were excluded of the analysis due to the following reasons: (i) not fitting the smoking status categories fixed for the study: 15; (ii) not providing saliva samples to biochemical analyses: 21; (iii) incongruence between smoking status report and cotinine salivary levels: 9; (iv) psychiatric disorders: 5; (v) organic comorbidities: 3; (vi) intellectual difficulties to understand several questions: 6.

The final sample consisted of 269 participants, 94 included in the SG and 175 in the NSG. Among the 94 smokers, 66 (70.2%) were called for a second assessment interview at the end of pregnancy. Most of these subjects assessed were evaluated in the third trimester, averaging 37.5 weeks. Twenty-three of them were evaluated after childbirth, with a median postpartum interval of 4.4 weeks. Due to technical problems, saliva cotinine measurements were not available for checking the self-reported smoking status at the second interview.

The SG reported that it had started smoking at a mean age of 14.9±3.0 years, and a mean smoking history of 13±5.9 years. The SG smoked, on average, 11±9.2 cigarettes a day, and its mean FTND was 4.4±2.3, indicating, on average, addiction to nicotine of moderate degree.

Both groups showed gestational ages around 15 weeks (Table 1). Smoking during pregnancy was associated with a higher number of previous pregnancies and spontaneous abortions. Cigarette consumption was also associated with older age. Regarding intention to become pregnant, beinga smoker was associated with

Table 1. Socio-demographic features and obstetric history of pregnant women according to their smoking status.

	Smokers (n = 94)	Non-Smokers (n = 175)	OR	95% CI	p
Age (years)	28.4 ± 5.5	25.7 ± 5.6	1.09	1.04-1.14	<0.001
Gestational age (weeks)	15.0 ± 5.1	14.6 ± 4.8	1.02	0.97-1.07	0.498
Pregnancies	3.5 ± 1.6	2.1 ± 1.1	1.86	1.57-2.21	<0.001
Spontaneous abortions	0.6 ± 0.8	0.2 ± 0.5	2.36	1.60-3.48	<0.001
Ratio abortions/pregnancies	0.1 ± 0.2	0.1 ± 0.1	8.07	1.91-34.08	0.005
Pregnancy intention[+]					
Planned	40 (43%)	82 (47%)	0.49	0.28-0,87	0.012
Unplanned	9 (10%)	49 (28%)	0.19	0.08-0,44	<0.001
*Unwanted to be a mother**	44 (47%)	44 (25%)	1	-	-
Marital status					
Living without a partner	27 (29%)	28 (16%)	2.12	1.15-3.90	0.014
*Living with a partner**	67 (71%)	147 (84%)	1	-	-
Employed					
Yes	28 (30%)	95 (54%)	0.36	0.21-0.62	<0.001
*No**	66 (70%)	80 (46%)	1	-	-
Attended school years					
< 8	46 (49%)	21 (12%)	10.18	4.31-24.07	<0.001
8-11	31 (33%)	75 (43%)	1.92	0.98-3.79	0.055
*≥ 12**	17 (18%)	79 (45%)	1	-	-
Economic class					
B	12 (13%)	40 (23%)	0.37	0.15-0.89	0.021
C	59 (63%)	108 (62%)	0.67	0.35-1.28	0.225
*D/E**	22 (24%)	27 (15%)	1	-	-

*Reference category; [+]Data available for 93 smokers.

smaller chances of having a planned or an unplanned pregnancy. Pregnant smokers also showed smaller chances of being employed and belonging to the highest economic class. In addition, smoking during pregnancy was associated with having under eight years of education and to living without a partner (Table 1).

Pregnant women who smoked exhibited higher chances of drinking alcohol and using illicit drugs in the previous month. They also showed higher chances of having tried cannabis along their lives, and to be subject to passive smoking at home (Table 2).

Concerning the psychological features, the SG showed significant higher chances of exhibiting higher scores on anxiety, depression and perceived stress (Table 3). Both groups showed similar records of maternal-fetal attachment. Neuroticism was the only factor of personality associated with smoking during pregnancy (Table 3).

Adjusted analyses of all variables for confounding factors did not generate significant changes in the OR values initially identified.

Mean number of daily smoked cigarettes did not significantly change between the first and second interview (11.7±9.3 X 8.9±7.5). Thirty-two (48.5%) women reduced the number of cigarettes smoked a day, while four (6.1%) quit smoking by late pregnancy. Thirty (45.4%) women kept smoking the same amount, or even increased the number of cigarettes smoked a day. The univariate logistic regression model did not detect any significant association between basal socio-demographic or psychological features with qualitative changes in smoking behavior at the end of pregnancy (Table 4).

Table 2. Use of alcohol, illicit drugs, and passive smoking in pregnant women according to their smoking status.

	Smokers (n = 94)	Non-Smokers (n = 175)	OR	95% CI	p
Drinking in the past month					
Yes	52 (55%)	33 (19%)	5.33	2.92-9.71	<0.001
*No**	42 (45%)	142 (81%)	1	-	-
Use of illicit drugs in the past month					
Yes	5 (5%)	1 (1%)	9.78	1.13-89.95	0.019
*No**	89 (95%)	174 (99%)	1	-	-
Past experimentation with cannabis					
Yes	75 (81%)	32 (18%)	18.62	8.30-41.77	<0.001
*No**	18 (19%)	143 (82%)	1	-	-
Use of cannabis in the past month[+]					
Yes	15 (16%)	0			
*No**	78 (84%)	175 (100%)	-	-	-
Passive smoking at home					
Yes	51 (54%)	34 (19%)	4.92	2.72-8.89	<0.001
*No**	43 (46%)	141 (81%)	1	-	-
Passive smoking at the workplace[++]					
Yes	3 (11%)	13 (14%)	1.45	0.52-4.01	0.474
*No**	24 (89%)	77 (86%)	1	-	-

*Reference category; [+]Data available for 93 smokers; [++]Data available for 27 smokers and 90 non-smokers.

Table 3. Psychological features of pregnant women according to their smoking status.

	Smokers (n = 94)	Non-Smokers (n = 175)	OR	95% CI	p
Anxiety	10.1 ± 4.66	7.0 ± 4.33	1.15	1.09-1.21	<0.001
Depression	8.3 ± 3.94	6.1 ± 3.48	1.17	1.09-1.25	<0.001
Perceived stress	24.7 ± 9.36	18.5 ± 8.87	1.07	1.04-1.10	<0.001
Maternal-fetal attachment	75.8 ± 17.81	78.3 ± 13.44	0.99	0.97-1.01	0.190
Factors of personality					
Agreeableness	20.7 ± 3.86	20.3 ± 3.01	1.03	0.96-1.11	0.397
Conscientiousness	22.0 ± 2.84	22.3 ± 2.82	0.97	0.88-1.06	0.457
Neuroticism	16.4 ± 4.45	14.0 ± 4.71	1.11	1.06-1.18	<0.001
Openness	14.9 ± 5.03	14.6 ± 4.14	1.02	0.96-1.08	0.557
Extraversion	18.1 ± 4.85	17.0 ± 4.40	1.05	0.99-1.11	0.080

Table 4. Results of univariate logistic regression model evaluating potential predictors of qualitative changes on smoking status at the end of pregnancy.

	OR*	95% CI	p
Age	0.98	0.89-1.07	0.664
Marital status	1.16	0.41-3.31	0.772
Employment	0.97	0.34-2.79	0.961
Attended school years	1.29	0.67-2.48	0.440
Economic class	0.38	0.10-1.41	0.148
Intention to get pregnant	1.38	0.82-2.31	0.223
Drinking in the past month	0.70	0.26-1.85	0.472
Past experimentation with cannabis	0.82	0.25-2.68	0.745
Use of cannabis in the past month	0.37	0.09-1.57	0.179
Passive smoking at home	1.05	0.39-2.77	0.928
Smoking years	0.98	0.91-1.07	0.718
Cigarettes smoked a day	0.98	0.93-1.04	0.501
Test of Fargerström	1.07	0.87-1.33	0.484
Anxiety	0.98	0.87-1.09	0.706
Depression	1.08	0.95-1.24	0.238
Perceived stress	1.01	0.95-1.07	0.662
Maternal-fetal attachment	0.98	0.96-1.01	0.258
Agreeableness	1.02	0.89-1.16	0.775
Conscientiousness	0.92	0.76-1.11	0.397
Neuroticism	1.07	0.96-1.19	0.231
Openness	0.93	0.84-1.02	0.112
Extraversion	0.96	0.87-1.05	0.396

*Dependent variables: quit smoking/decrease smoking (n=36) versus stability/increase smoking (n=30).

DISCUSSION

The present results indicate that smoking during pregnancy is associated with a set of socio-demographic variables. Pregnant smokers were older, had less schooling and a greater number of previous gestations and abortions. In addition, they were more likely to use alcohol, illicit drugs and to be exposed to passive cigarette smoke at home. On the other hand, having a better economic class, being employed, and having a planned or unplanned pregnancy were negatively associated with smoking. Regarding psychological features, pregnant smokers exhibited higher scores of anxiety, depression, perceived stress, and personality with elevated degree of Neuroticism.

Smoking is mediated, among others, by social contexts which place individuals at greater risk of adopting risky habits. For instance, low levels of educational attainment would be associated with less knowledge and perception of the harms of smoking.[27] Low levels of education are also associated with adoption of poorly adapted coping strategies for stressful events.[28] It is possible that pregnant women with low educational levels lack a repertoire of effective strategies for dealing with daily stress and use cigarettes as a way to regulate its effects.

Low economic status is a recognized risk factor for smoking in general and during pregnancy. Thus, the present results confirm previous findings. Although some studies have not identified an association between unemployment and smoking in pregnancy, the results of this study agree with several others.[18-20] It is important to recognize that low economic status, poor education and unemployment tend to run together.

Cases and controls also showed differences regarding the number of previous pregnancies and miscarriages. Several studies have confirmed the association between smoking and multiparity.[12,17] However, this association could be only expression of poorer educational conditions. The abortions/pregnancies ratio was employed here as a way to correct the number of miscarriages for the variable amount of pregnancies exhibited by the volunteers. Although smoking is a well-known factor for spontaneous abortions, these results preclude making causal assumptions, mainly because they are about current smoking in pregnancy and past history of miscarriages. However, it is fair to assume that these women possibly smoked in previous pregnancies, contributing to a higher number of abortions among them.

Using the category "unwanted to be mother" as a reference in analysis, it was observed an inverse association between both, "planned" and "unplanned" pregnancies, with smoking. This suggests that the desire to become pregnant, even if it is an unplanned one, may decrease the chances of smoking among women.

Pregnant women living without a partner exhibited higher chances to be smokers. Such results agree with previous literature, and may be attributed, at least in part, to worsen socioeconomic status and poor schooling among single mothers.[20,29] Besides, pregnant women

without a partner may lack the necessary emotional support for dealing with issues during the pregnancy, making smoking cessation difficult.

Pregnant women who smoked showed higher chances of referring passive smoking at home, and this may only reflect the finding that smoking tend to concentrate in certain social environments. However, it may also represent a lack of knowledge about the risks of second-hand smoking even in the pregnancy.

The identification of socio-demographic variables linked to smoking during pregnancy should be taken into account when planning anti-tobacco interventions for pregnant women. The association between less schooling and smoking, for example, shows that these women may have greater difficulties in understanding the value of quitting during pregnancy, and the strategies that lead to cessation. The association between smoking and living without a partner suggests that these women may benefit from social support such as group interventions.

The relation between smoking in pregnancy with the consumption of alcohol and illicit drugs, mainly marijuana, was not unexpected, since these associations have been frequently described. As cigarettes and alcohol are legal substances, even in pregnancy, they are more detectable through self-report than illicit substances. Therefore, the identification of smoking by pregnant women, should point to health care providers the need to inquire about the use of illicit drugs.

This is the first study that investigated personality traits in Brazilian pregnant smokers. Personality trait is defined as an individual predisposition that determines a tendency to exhibit consistent patterns of thoughts, feelings, and behaviors.[30] The present finding linking Neuroticism with smoking has already been reported, although negative associations with Extraversion, Conscientiousness or Socialization were not found at this time.[5] High scores on Neuroticism are linked to a propensity to experience negative states such as tension, depression, frustration, guilt, insecurity, and difficulties in coping with stressful situations. Moreover, such individuals seem to have a poorly adapted pattern in their choice of coping strategies. Some studies suggest that high scores on Neuroticism are related to use of ineffective coping strategies such as emotion-focused coping.[31,32]

In this sense, personality could act on smoking behavior as a way of selecting situations in which smoking would be most reinforcing, depending on the personality traits. For people with high Neuroticism scores, smoking will be more pleasurable because of its immediate anxiolytic and relaxing effects.[33] The association of Neuroticism with smoking comes closer to an explanatory model of self-medication, in which is assumed that neurotics, having a tendency to negative states, would be better able to develop nicotine dependence, because they found in it a way to alleviate these affects.[34] At the same time, paradoxically, there are evidences that smoking can aggravate such states, which would therefore be expressed in a "more" neurotic personality type.[35]

The present study did not find an association between smoking status and the degree of maternal-fetal attachment. Nevertheless, smoking in pregnancy was associated with higher levels of negative affect, including anxiety, depression and perceived stress. These are well known associations, but the basis of the phenomena are not completely clear.[11,13,36] Negative affect could be a causal explanation and predispose people to smoke.[37,38] However, paradoxically, there are reports that former smokers exhibit fewer symptoms of anxiety, depression, and lower stress levels compared to baseline measurements.[39,40] On the other hand, it is common for women to represent cigarette smoking as an effective way to deal with negative states. Moreover, pregnancy involves increases of anxious and depressed states due to hormonal changes, as well as it represents a phase which carries a higher overall stress load. Among pregnant women who were established smokers, and probably used cigarettes as an apparatus to deal with personal difficulties, it is speculated that this pattern will continue during pregnancy.

The findings of this study involving associations of smoking in pregnancy with anxiety, depression, perceived stress and Neuroticism are important elements to be addressed in cessation interventions. It points to the need to educate women about the potential role of smoking on worsening negative states, and learning appropriate behaviors to deal with anxiety, depression, and stress. Strategies to reduce negative states, such as relaxation and exercise, constitute some components that could be emphasized into cessation approaches among pregnant women. In addition, intervention groups limited to pregnant women could increase their motivation to quit, as they would be placed in a judgment-free and more identifiable environment.

This study also investigated eventual associations between social and psychological characteristics in early pregnancy and changes in smoking habits at the time of delivery. Only four women quit smoking, and a univariate logistic regression model involving potential predictors of qualitative changes in smoking status did not find any significant item. It is important to recognize that the number of women interviewed at the end of pregnancy was small and insufficient to obtain definitive answers.

This study exhibits several limitations. An active search strategy was adopted to locate pregnant smokers through data from electronic medical records and information from nurses. While this made possible an acceptable number of pregnant smokers, it inserted a convenience sampling bias. On the other hand, very strict criteria were adopted to define smoking status. Thus, information of occasional smokers and women who changed their smoking status in the six months prior to pregnancy diagnosis was not obtained. In this context, the results of this study reflect more the findings of well-established smokers compared to

non-smokers. The CG included both never smokers and ex-smokers, what may also have influenced the final results. Lost to follow-up prevented a second evaluation of all smokers initially assessed. Although smoking status was verified for every volunteer through biochemical assessment at first assessment, the same was not possible for the participants by late pregnancy.

In conclusion, smoking during pregnancy is associated with more unfavorable social conditions. Pregnant smokers exhibit a higher number of pregnancies and miscarriages, and are also more prone to engage in health risky behaviors, like drinking and use of illicit drugs. Psychological variables associated with smoking suggest that pregnant smokers exhibit more negative psychological states than nonsmokers, including a personality profile of accentuated Neuroticism. It is advisable to take all these factors in account when designing anti-tobacco interventions specifically for this group of women. None of the investigated psychological variables could predict smoking changes during pregnancy.

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AUTHOR CONTRIBUTIONS

ATLF: conceived study design, collected data, organized data for statistical analysis, interpreted results, wrote manuscript. ALRJ: contributed for study design, performed statical analysis, wrote manuscript. NCG: performed bioquemical analysis and interpretation, wrote manuscript. BSM: performed bioquemical analysis and interpretation, wrote manuscript. JABM: conceived study design, coordinated data collection, organized final data for statistical analysis, interpreted results, wrote manuscript.

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Use of hydroxychloroquine to prevent SARS-CoV-2 infection and treat mild COVID-19: a systematic review and meta-analysis

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ABSTRACT

Objective: Chloroquine or hydroxychloroquine has demonstrated no effect on the treatment of hospitalized COVID-19 patients. This study aimed to answer questions related to the use of hydroxychloroquine for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection and in the treatment of patients with mild COVID-19 in terms of hospitalization, adverse events, and mortality. **Methods:** This was a systematic review and meta-analysis of phase 3 randomized clinical trials, selected from various databases, which compared patients who received hydroxychloroquine for SARS-CoV-2 prophylaxis or treatment of mild COVID-19 cases with controls. **Results:** A total number of 1,376 studies were retrieved. Of those, 9 met the eligibility criteria and were included in the study. No statistically significant differences were found between the hydroxychloroquine and control groups in terms of pre- or post-exposure prophylaxis of SARS-CoV-2 infection. The use of hydroxychloroquine increased the risk of adverse events by 12% (95% CI, 6-18%; $p < 0.001$), and the number needed to harm was 9. In addition, no significant differences were found between the hydroxychloroquine and control groups regarding hospitalization (risk difference [RD] = −0.02; 95% CI, −0.04 to 0.00; $p = 0.14$) or mortality (RD = 0.00; 95% CI, −0.01 to 0.02; $p = 0.98$) in the treatment of mild COVID-19. **Conclusions:** The use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection or treatment of patients with mild COVID-19 is not recommended.

Keywords: Hydroxychloroquine; COVID-19; SARS-CoV-2.

INTRODUCTION

COVID-19 is caused by SARS-CoV-2, which emerged in China in December of 2019, and has been declared a pandemic by the World Health Organization. The economy of each country is represented by the impairment in the rate of infected cases and mortality in the population, along with access to vaccines against SARS-CoV-2, and the national policies implemented to reduce airborne transmission are represented by the load on the health care system.[1] In this context, empiric pharmacological treatment strategies to prevent or control the progression of COVID-19 have been debated in different scenarios and discussed in the scientific literature.[2,3]

COVID-19 is a novel disease that required implementing rapid treatment proposals to reduce transmission, protecting exposed subjects, and decreasing mortality. The use of chloroquine or hydroxychloroquine has been suggested for reducing viral load and controlling disease severity.[4] However, after over a year of living with the COVID-19 pandemic, we have accumulated scientific evidence stating that the use of hydroxychloroquine is futile for treating hospitalized COVID-19 patients. Indeed, the actual treatment guidelines are supported by the premise of the best medical evidence, and there is none to support the use of hydroxychloroquine to reduce the need for mechanical ventilation or all-cause mortality rate.[5] Conversely, there are places where the routine use of hydroxychloroquine is still being recommended as an optimal intervention to prevent infection in subjects with a high risk of contamination (pre-exposure prophylaxis or post-exposure prophylaxis) or to control severity progression of COVID-19 after an infection. Moreover, there are no systematic reviews assessing the use of hydroxychloroquine in patients with mild COVID-19. Therefore, there is a lack of knowledge to determine whether chloroquine or hydroxychloroquine can prevent SARS-CoV-2 infection or control COVID-19 severity in non-hospitalized patients. The objective of the present study was to collect and evaluate evidence from the literature regarding these topics and to provide treatment recommendations. To that end, we addressed the following clinical questions: "Does hydroxychloroquine prevent illness in individuals who have not been diagnosed with COVID-19 but have had contact with an infected individual?" and "Does hydroxychloroquine reduce the chances of hospitalization, the development of adverse events, or the risk of mortality in patients with mild COVID-19?"

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METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[6]

Eligibility criteria

The protocol of this study was based on the **P**atients of interest, **I**ntervention to be studied, **C**omparison of intervention, and **O**utcome of interest (PICO) methodology. Regarding the prophylactic use of hydroxychloroquine, the PICO framework was as follows: Patients: pre-exposure (not diagnosed with COVID-19) or post-exposure (positive RT-PCR for SARS-CoV-2) patients; Intervention: use of hydroxychloroquine; Comparison: standard treatment or placebo; and Outcome: individuals with positive RT-PCR tests, hospitalization (ward or ICU admission), mortality, and adverse events. We also investigated beneficial or harmful outcomes due to the use of hydroxychloroquine in adults at risk for SARS-CoV-2 infection. Health care workers at hospital-based units were considered at risk for being infected. Regarding patients with mild COVID-19, the PICO framework was as follows: Patients: patients with a confirmed positive RT-PCR test who had not been hospitalized prior to randomization; Intervention: use of hydroxychloroquine; and Comparison: standard treatment or placebo; and Outcome: hospitalization (ward or ICU admission), mortality, and adverse events.

The eligibility criteria for the inclusion of studies were phase 3 randomized controlled trials (RCTs) and phase 3 RCTs systematically reviewing the PICO questions. We imposed no restrictions regarding date of publication, language, or full-text availability.

Information sources and search strategy

Two of the authors developed the search strategy, which was revised and approved by the team, selected information sources, and systematically searched the following databases: MEDLINE, EMBASE, Central Cochrane, and ClinicalTrials.gov. Specific search strategies were used for each database: 1: ("COVID" OR "COV" OR "coronavirus" OR "SARS"); 2: ("chloroquine" OR "chlorochin" OR "hydroxychloroquine" OR "oxychloroquine" OR "hydroxychlorochin") 3: 1 AND 2; and 4: 3 AND (Random*).

Study selection

Two independent researchers selected and extracted the data from the included studies. First, the articles were selected based on the title and abstract. Second, full texts were evaluated in order to include or exclude the studies; disagreements were resolved by consensus.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (hydroxychloroquine and control), outcomes, and follow-up period were extracted from the studies.

Regarding prophylaxis with hydroxychloroquine, the results (outcomes) collected were positive RT-PCR (longer follow-up), hospitalization, adverse events, severe adverse events, and mortality. Regarding treatment of mild COVID-19 cases with hydroxychloroquine, the outcomes were hospitalization, adverse events, severe adverse events, and mortality. Control groups varied among the studies.

Risk of bias and quality of evidence

The risk of bias was assessed using the Cochrane risk-of-bias (RoB 2)[7] tool as were other fundamental elements, being expressed as very serious, serious, or non-serious. The quality of the evidence was extrapolated from the risk of bias and was described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology as very low, low, or high, and, for meta-analyses, it was described by the GRADEpro Guideline Development Tool (GDT; McMaster University, Hamilton, ON, Canada), as very low, low, moderate, or high.

Synthesis of results and analysis

Categorical outcomes were expressed by group (hydroxychloroquine and control), number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference between the groups was significant, a 95% CI was expressed on the basis of the number needed to treat or the number needed to harm (NNH). We used fixed-effect meta-analysis to evaluate the effect of hydroxychloroquine vs. control on the outcomes when those data were available in at least two RCTs considered to have homogeneous study characteristics. Effects of meta-analyses were reported as risk differences (RD) and corresponding 95% CIs; a 95% CI including the number 0 in its range meant that there was no difference in the outcome effect between the hydroxychloroquine and control arms. The use of RD shows the absolute effect size in the meta-analysis when compared with relative risk (RR) or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. Heterogeneity of effects among studies was quantified with the I^2 statistic (an $I^2 > 50\%$ means high heterogeneity). For the meta-analysis, we used the Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

A total of 1,376 studies were retrieved from the selected databases (Figure 1). After eliminating duplicates and including studies that met the eligibility criteria, 58 studies were selected for the assessment of their full texts (MEDLINE: 51; EMBASE: 4; and ClinicalTrials.gov: 3). Of those, 49 studies were excluded. Therefore, 9 RCTs[8-16] were selected, whose characteristics (Table 1), results, risk of bias, quality of evidence, and synthesis of evidence are described below (Tables 2-5).

We assumed that the risk of bias in the studies selected to support the conclusions on the treatment was not serious. The quality of evidence in the analysis of prophylaxis varied according to the analyzed outcome: diagnosis of COVID-19 (moderate), hospitalization (moderate), adverse events (very low), serious adverse events (very low), and mortality (moderate). The quality of evidence in the analysis of mild COVID-19 treatment varied according to the analyzed outcome: hospitalization (high), adverse events (very low), serious adverse events (high), and mortality (high).

Hydroxychloroquine for pre- or post-exposure prophylaxis of SARS-CoV-2 infection

The follow-up period ranged from 2 to 8 weeks in the studies selected. No statistically significant difference was found regarding the incidence of positive COVID-19 results (RT-PCR) between the hydroxychloroquine and control groups for pre- or post-exposure prophylaxis of SARS-CoV-2 infection during the follow-up period (RD = 0.01; 95% CI, −0.01 to 0.02; p = 0.13; Figure 2A). The RR was 1.19 (95% CI, 0.95-1.50). The quality of evidence was moderate (Table 4).

There was no significant difference between the hydroxychloroquine and control groups regarding the incidence of hospitalization during the follow-up period (RD = −0.00 [95% CI, −0.01 to −0.00]; p = 0.26; Figure 2B; and RR = 0.74 [95% CI, 0.44-1.25]). The quality of evidence was moderate (Table 4). The use of prophylactic hydroxychloroquine increased the risk of adverse events by 12% (95% CI, 6-8%; p < 0.001; NNH = 9) when compared with the control group (RR = 1.69 [95% CI, 1.36-2.09]; Figure 2C). However, the quality of evidence was very low (Table 4).

In terms of the incidence of serious adverse events, no statistically significant difference was found between the hydroxychloroquine and control groups (RD = 0.00 [95% CI, −0.01 to 0.01]; p = 0.77; Figure 2D; and RR = 1.70 [95% CI, 0.91-3.17]). The quality of evidence was very low (Table 4). Likewise, no statistically significant difference was found regarding the incidence of mortality between the groups (RD: −0.00 [95% CI, −0.00 to 0.00]; p = 0.51; Figure 2E; and RR = 0.66 [95% CI, 0.22-2.02]). The quality of evidence was moderate (Table 4).

Hydroxychloroquine for treating mild COVID-19

When we compared the hydroxychloroquine and control groups that included patients with mild COVID-19, no statistical differences (Figure 3) were found regarding hospitalizations (RD = −0.02 [95% CI, −0.04 to 0.00]; p = 0.14; Figure 3A; and RR = 0.68 [95% CI, 0.41-1.14]), with high quality of evidence (Table 5); adverse events (RD = 0.11 [95% CI: −0.09 to 0.31]; p = 0.27; Figure 3B; and RR = 1.47 [95% CI, 0.79-2.72]), with very low quality of evidence (Table 5); serious adverse events (RD = −0.00 [95% CI, −0.04 to 0.04]; p = 0.95); Figure 3C; and RR = 0.97 [95% CI, 0.44-2.16]); and mortality (RD = 0.00 [95% CI, −0.01 to 0.01]; p = 0.98; Figure 3D; and RR = 1.07 [95% CI, 0.15-7.86]), both with high quality of evidence (Table 5).

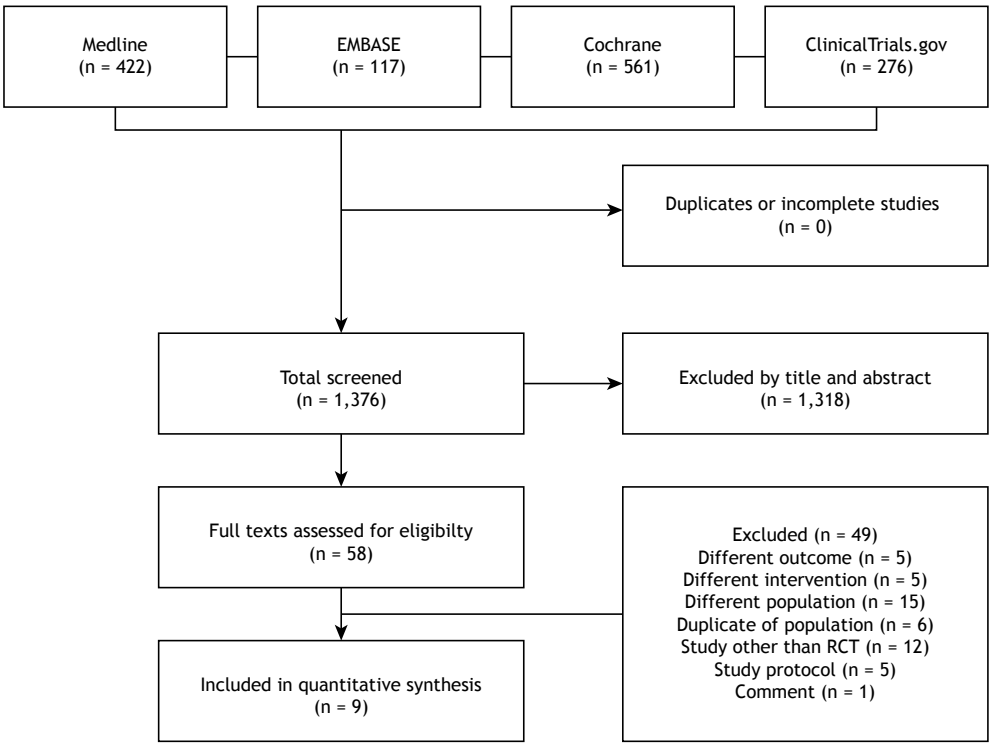

Figure 1. Flow chart of the selection process in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations. RCT: randomized clinical trial.

Table 1. Description of the studies included. (Continue...)

Study/ country	Participants (N)	Type/ identifier	Context	Eligibility criterion	Group	Outcome	Follow-up period
Abella et al.[8] United States of America	132	Parallel RCT NCT04329923	Post-exposure prophylaxis	Health care workers at COVID-19 units and no previous SARS-CoV-2 infection within the last 2 weeks	Placebo vs. Hydroxychloroquine, 600 mg/day for 8 weeks	- Positive test for SARS-CoV-2 during 8 weeks - Adverse events	8 weeks
Mitjà et al.[10] Spain	2,485	Cluster RCT NCT04304053	Post-exposure prophylaxis	Health care workers, household contacts, and nursing home workers or residents with no previous SARS-CoV-2 infection within the last 2 weeks	Usual care vs. Hydroxychloroquine, 800 mg on day 1, followed by 600 mg/day for 6 days	- Symptoms and positive test for SARS-CoV-2 - Hospitalization - Adverse events - Death	4 weeks
Boulware et al.[12] Unites States of America and Canada	821	Parallel RCT NCT04308668	Post-exposure prophylaxis	Household or occupational exposure to individuals with confirmed COVID-19 (distance ≤ 6 ft for >10 min with an infected subject or no use of face mask or eye shield)	Placebo vs. Hydroxychloroquine, 800 mg on day 1 and 600 mg within 6-8 h after the first dose, followed by 600 mg/day for 4 days	- Positive test for SARS-CoV-2 - Hospitalization - Adverse events - Deaths	2 weeks
Rajasingham et al.[11] United States of America and Canada	1,483	Parallel RCT NCT04328467	Pre-exposure prophylaxis	Health care workers with high risk for SARS-CoV-2 exposure (ICU, ER, COVID-19 units)	Placebo (folic acid) vs. Hydroxychloroquine, 400 mg on day 1 and 400 mg 6-8 h later, followed by 400 mg once a week for 12 weeks vs. Hydroxychloroquine, 400 mg on day 1 and 400 mg 6-8 h later, followed by 400 mg twice a week for 12 weeks	- COVID-19 free (no symptoms or negative RT-PCR result) - Hospitalization - Adverse events - Death	12 weeks
Barnabas et al.[9] United States of America	689	Parallel RCT NCT04328961	Post-exposure prophylaxis	Contact with an index case diagnosed SARS-CoV-2 infection within 96 h	Placebo vs. Hydroxychloroquine, 400 mg for 3 days, followed by 200 mg/day for 11 days	- Positive test for SARS-CoV-2 - Adverse events	14 days
Omrani et al.[14] Qatar	456	Triple parallel RCT NCT04349592	Outpatients with mild COVID-19	Mild disease or no symptoms, outpatients	Placebo vs. Hydroxychloroquine, 600 mg/day for 1 week vs. Hydroxychloroquine, 600 mg/day for 1 week + azithromycin	- Viral load - Hospitalization - Severe adverse events - Death	14 days

Continue ►

Table 1. Description of the studies included. (Continuation...)

Study/ country	Participants (N)	Type/ identifier	Context	Eligibility criterion	Group	Outcome	Follow-up period
Reis et al.[13] Brazil	685	Triple parallel RCT NCT04403100	Mild COVID-19	Outpatients reporting less than 8 days since onset of flu-like symptoms or chest CT consistent with COVID-19	Placebo vs. Hydroxychloroquine, 800 mg as a loading dose, followed by 400 mg daily for 9 days vs. Lopinavir-ritonavir loading dose of 800 mg and 200 mg, respectively, every 12 h, followed by 400 mg and 100 mg, respectively, every 12 h for the following 9 days	- Adverse events - Severe adverse events - Hospitalization - Deaths	90 days
Mitjà et al.[15] Spain	293	Parallel RCT NCT04304053	Mild symptoms of COVID-19	Outpatients; symptoms for less than 5 days prior to enrollment	Usual care vs. Hydroxychloroquine, 800 mg on day 1, followed by 400 mg/day for 6 days	- Viral load - WHO progression scale - Hospitalization - Severe adverse events - Deaths	28 days
Skipper et al.[16] United States of America and Canada	491	Parallel RCT NCT04308668	Mild COVID-19	Outpatients, positive SARS-CoV-2 test and symptoms for ≤ 4 days or compatible symptoms after high-risk exposure to a contact with PCR-confirmed SARS-CoV-2 within the last 14 days	Placebo vs. Hydroxychloroquine, 800 mg once and 600 mg in 6-8 h, followed by 600 mg daily for another 4 more days	- Hospitalization - Adverse events - Deaths	14 days

RCT: randomized controlled trial.

Table 2. Risk of bias of the individual studies included on the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection.

Study	Year	Randomization	Blinding/ Allocation concealment	Double blinding	Blinding of outcome assessors	Loss	Prognostic characteristic	Appropriate outcome	Intention-to-treat analysis	Sample size calculation	Early interruption
Abella et al.[8]	2021	Low	Low	Low	Uncertain	Low	High	Low	High	Low	Low
Barnabas et al.[9]	2021	Low	Low	Low	Uncertain	High	Uncertain	Low	High	Low	Low
Mitjà et al.[10]	2021	Low	Low	High	Uncertain	Low	Low	Low	High	Low	Low
Rajasingham et al.[11]	2020	Low	Low	Low	Uncertain	Low	Low	Low	High	Low	Low
Boulware et al.[12]	2020	Low	Low	Low	Uncertain	Uncertain	High	Low	Uncertain	High	Low

Table 3. Risk of bias of the individual studies included on the treatment of mild COVID-19 patients with hydroxychloroquine.

Study	Year	Randomization	Blinding/ Allocation concealment	Double blinding	Blinding of outcome assessors	Loss	Prognostic characteristic	Appropriate outcome	Intention-to-treat analysis	Sample size calculation	Early interruption
Reis et al.[13]	2021	Low	Low	Low	Uncertain	Low	Low	Low	Low	Low	Low
Omrani et al.[14]	2020	Low	Low	Low	Uncertain	Low	Low	Low	Low	Low	Low
Mitjà et al.[15]	2020	Low	Low	High	Uncertain	Low	Low	Low	Low	Low	Low
Skipper et al.[16]	2020	Low	Low	Low	Uncertain	Low	Low	Low	Low	Low	Low

DISCUSSION

The main results of this systematic review showed that the use of hydroxychloroquine for pre- or post-exposure prophylaxis of SARS-CoV-2 had no effect on the incidence rate of confirmed SARS-CoV-2 positivity and that its use increased the risk of adverse events by 12%. In addition, the use of hydroxychloroquine in mild COVID-19 patients caused no significant differences in the rates of hospitalization, adverse events, and mortality.

The choice of relevant clinical outcomes is fundamental in defining the effectiveness of a medical treatment, and this is also true for COVID-19. treatment. For potential COVID-19 patients, prophylaxis is essential to prevent disease, and the treatment of patients with mild COVID-19 is necessary to prevent hospitalization (ward or ICU admission) and disease progression.

Our results are similar to those of a previous systematic review comprising two RCTs that studied the use of hydroxychloroquine for pre- or post-exposure prophylaxis against SARS-CoV-2 infectio.[17-19] However, this is the first review that studied the use of hydroxychloroquine only in patients with mild COVID-19 to assess disease progression. Our systematic review included one more RCT than did a study by Lewis et al.[19] to evaluate the efficacy of pre-exposure or post-exposure prophylaxis with hydroxychloroquine. By adding that RCT to the analysis, we obtained results that were similar to those reported by Lewis et al.,[19] but we identified a decrease in the 95% CI related to risk. In other words, we reduced the uncertainty of pre- or post-exposure prophylaxis with hydroxychloroquine, and we reinforce the recommendation of not using hydroxychloroquine for that. Likewise, Hernandez et al.[18] described cohort studies and RCTs on the use of hydroxychloroquine as an intervention.

When we analyzed the results regarding the use of hydroxychloroquine in patients with mild COVID-19, most of the RoB 2 table items presented with a low risk of bias, and, concomitantly, the quality of evidence in most of the outcomes was high, which reinforces our final recommendation of not using hydroxychloroquine for the treatment of mild COVID-19 patients.

Phase 3 RCTs have several fundamental characteristics that guarantee the lowest degree of uncertainty when two forms of treatment or prophylaxis are compared: a. homogeneous samples in both groups are compared (patients with similar characteristics); b. allocation of patients to groups has no influence or interference by using random methods (unpredictability guarantees the same chance for any individual to be allocated to any of the groups); c. the population is represented (sample size estimation and power analysis that guarantees applicability and reproduction of results in practice); d. interventions are blinded (avoiding interference in the application of interventions); e. there is loss of control (avoiding manipulation in patient selection); f. procedures and interventions are standardized (avoiding variations in processes, doses, co-interventions, etc.);

Table 4. Table of evidence of the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection.
Question: Should hydroxychloroquine, when compared with controls, be used for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection?

Certainty assessment							Patient (n)		Effect		Certainty	Importance
Studies (n)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	CONTROL	Relative (95% CI)	Absolute (95% CI)		
POSITIVE RT-PCR												
6	randomized trials	serious[a,b,c,d,e]	not serious	not serious	not serious	none	148/3026 (4.9%)	124/3071 (4.0%)	RR 1.19 (0.95 to 1.50)	8 more per 1,000 (from 2 fewer to 20 more)	⊕⊕⊕◯ MODERATE	
HOSPITALIZATION												
4	randomized trials	serious[a,b,c,d,e]	not serious	not serious	not serious	none	24/2609 (0.9%)	33/2674 (1.2%)	RR 0.74 (0.44 to 1.25)	3 fewer per 1,000 (from 7 fewer to 3 more)	⊕⊕⊕◯ MODERATE	
ADVERSE EFFECTS												
4	randomized trials	serious[a,b,c,d,e]	very serious [f]	not serious	not serious	publication bias strongly suspected [g]	522/1756 (29.7%)	305/1731 (17.6%)	RR 1.69 (1.36 to 2.09)	122 more per 1,000 (from 63 more to 192 more)	⊕◯◯◯ VERY LOW	
SERIOUS ADVERSE EFFECTS												
4	randomized trials	serious[a,b,c,d,e]	very serious [f]	not serious	not serious	publication bias strongly suspected [g]	26/2548 (1.0%)	16/2603 (0.6%)	RR 1.70 (0.91 to 3.17)	4 more per 1,000 (from 1 fewer to 13 more)	⊕◯◯◯ VERY LOW	
DEATHS												
4	randomized trials	serious[a,b,c,d,e]	not serious	not serious	not serious	none	5/2609 (0.2%)	8/2674 (0.3%)	RR 0.66 (0.22 to 2.02)	1 fewer per 1,000 (from 2 fewer to 3 more)	⊕⊕⊕◯ MODERATE	

HCQ: hydroxychloroquine; and RR: Risk ratio.
Explanations
a. ABSENCE OF INTENTION-TO-TREAT ANALYSIS
b. UNBALANCED PROGNOSTIC CHARACTERISTICS BETWEEN THE GROUPS
c. ABSENCE OF SAMPLE CALCULATION
d. ABSENCE OF DOUBLE BLINDING
e. LOSSES OVER 20%
f. HETEROGENEITY GREATER THAN 75%
g. OUTLIER

Table 5. Table of evidence of the use of hydroxychloroquine for the treatment of mild COVID-19.
Question: Should hydroxychloroquine, compared with controls, be used for the treatment of mild COVID-19?

Certainty assessment							Patient (n)s		Effect		Certainty	Importance
Studies (n)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HCQ	CONTROL	Relative (95% CI)	Absolute (95% CI)		
HOSPITALIZATION												
4	randomized trials	not serious	not serious	not serious	not serious	none	23/714 (3.2%)	36/747 (4.8%)	RR 0.68 (0.41 to 1.14)	15 fewer per 1,000 (from 28 fewer to 7 more)	⊕⊕⊕⊕ HIGH	
ADVERSE EFFECTS												
2	randomized trials	not serious	very serious [a]	not serious	serious [b]	publication bias strongly suspected [c]	138/426 (32.4%)	92/438 (21.0%)	RR 1.47 (0.79 to 2.72)	99 more per 1,000 (from 44 fewer to 361 more)	⊕◯◯◯ VERY LOW	
SERIOUS ADVERSE EFFECTS												
3	randomized trials	not serious	not serious	not serious	not serious	none	11/502 (2.2%)	12/536 (2.2%)	RR 0.97 (0.44 to 2.16)	1 fewer per 1,000 (from 13 fewer to 26 more)	⊕⊕⊕⊕ HIGH	
DEATHS												
4	randomized trials	not serious	not serious	not serious	not serious	none	1/714 (0.1%)	1/747 (0.1%)	RR 1.07 (0.15 to 7.86)	0 fewer per 1,000 (from 1 fewer to 9 more)	⊕⊕⊕⊕ HIGH	

HCQ: hydroxychloroquine; and RR: Risk ratio.
Explanations
a. HETEROGENEITY GREATER THAN 75%
b. WIDE CI
c. OUTLIER

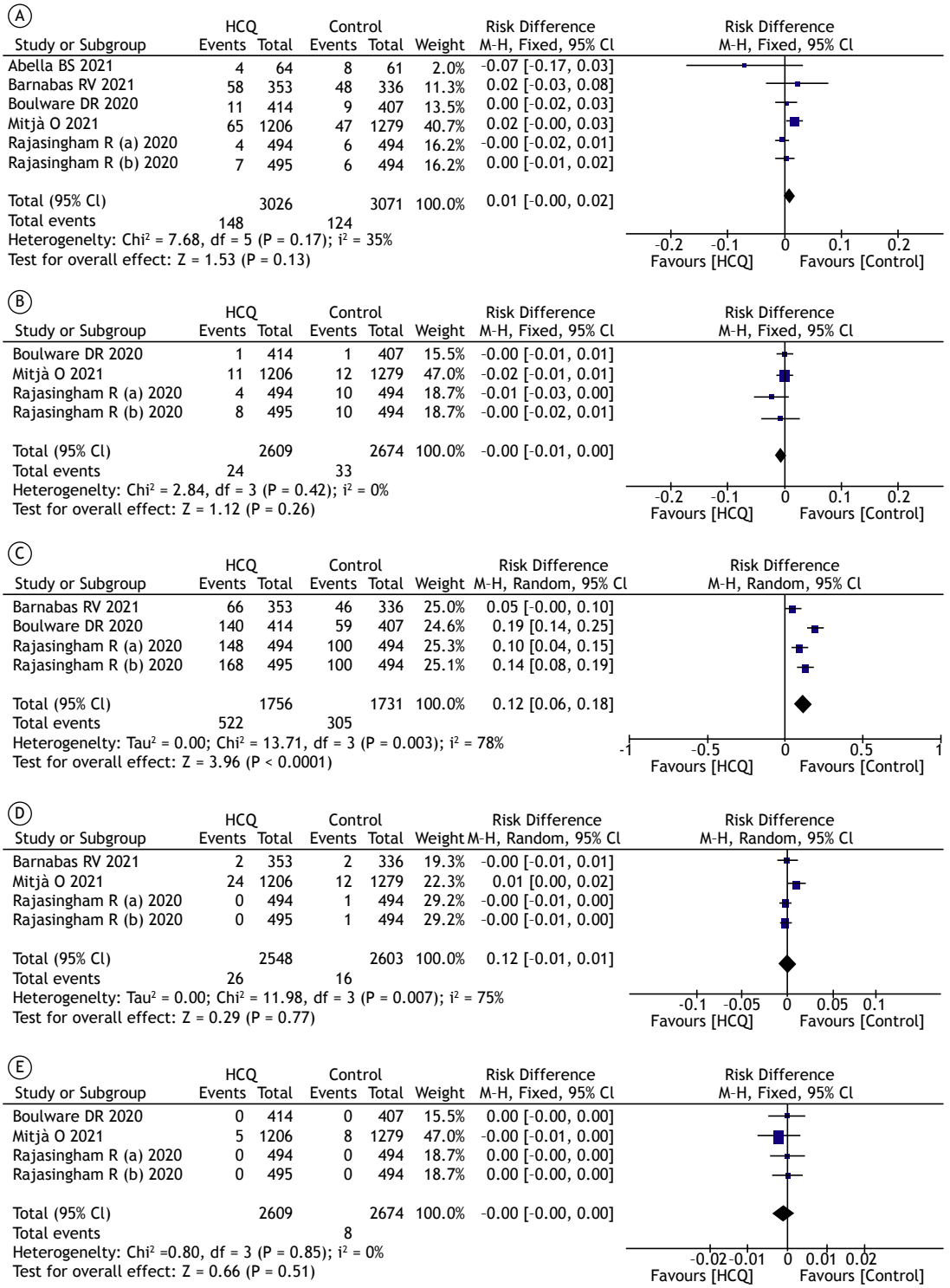

Figure 2. Comparison between hydroxychloroquine and control groups for prophylaxis of SARS-CoV-2 infection regarding the incidence of positive RT-PCR results (in A); hospitalization (in B); adverse events (in C); serious adverse events (in D); and deaths (in E). HCQ: hydroxychloroquine; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

and g. statistical analyses are performed directly using the number of events and averages, with no need for corrections. These characteristics are absent in comparative observational studies (cohort studies).

Several barriers can hamper the performance of RCTs, including three major barriers: 1. lack of patients (rare diseases); 2. technologies that are difficult to implement (incomparable, expensive, or complex); and 3. a long

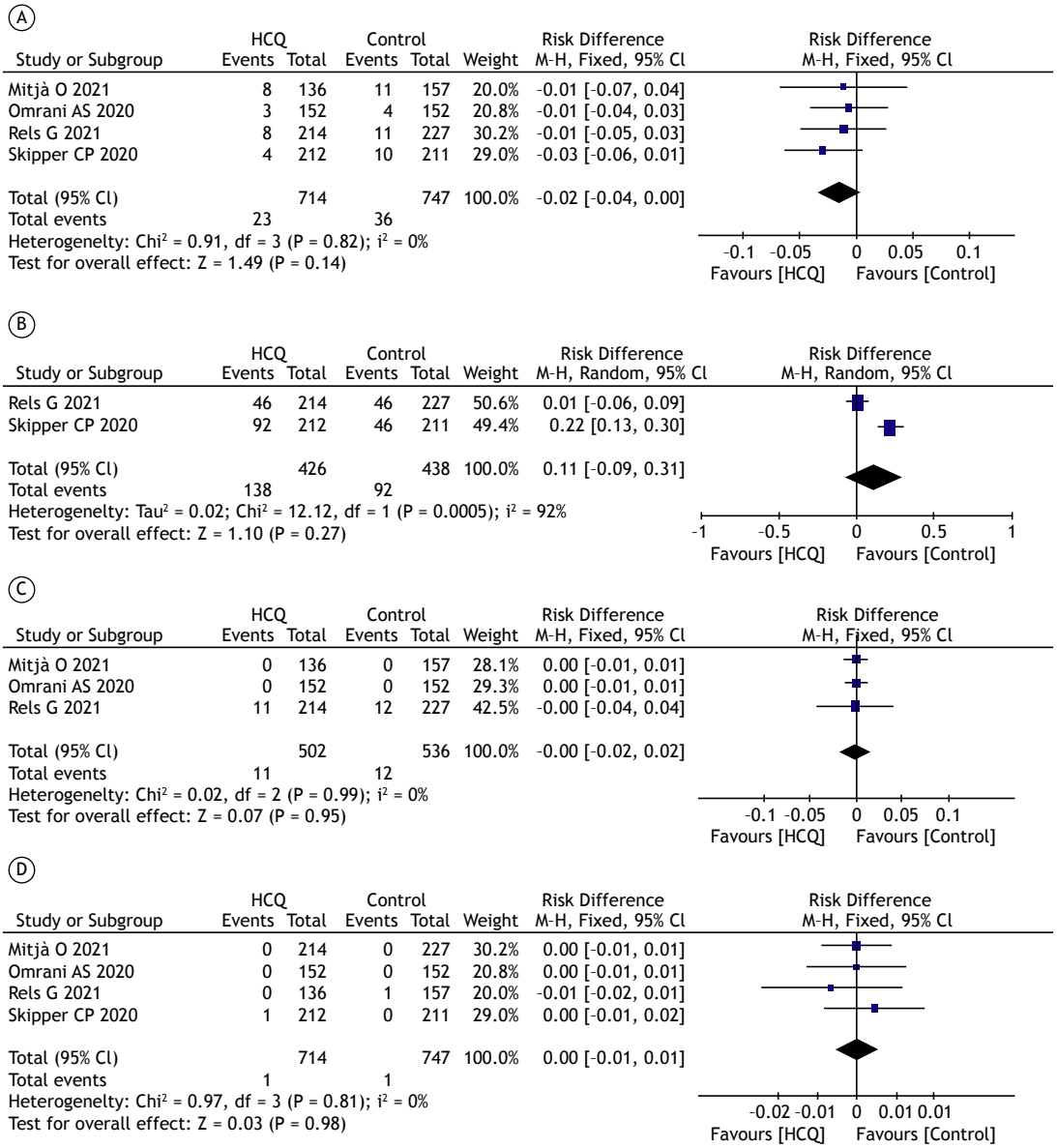

Figure 3. Comparison between hydroxychloroquine and control groups for the treatment of mild COVID-19 regarding the incidence of hospitalizations (in A); adverse events (in B); serious adverse events (in C);.and deaths (in D). HCQ: hydroxychloroquine; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

time for outcomes to occur (requiring a long follow-up period). However, this is not the case with COVID-19.

The available evidence can change over time. However, there is a considerable degree of certainty that can be conferred by individual RCTs or meta-analyses using such studies, which greatly reduces the likelihood that new studies will emerge and modify the conclusions. Therefore, the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection or for treatment of mild COVID-19 patients is unjustifiable and is currently contraindicated in order to avoid uncertainties and difficulties in making decisions.

The number of patients included in the present systematic review and meta-analysis is adequate, and the results are reproducible and can be applied in the management and care of patients.

This systematic review has limitations that need to be elucidated. First, we were unable to examine funnel plots to detect publication bias, given the small number of RCTs. However, we used a comprehensive search strategy. Second, we did not register or publish our protocol before, given the urgency to demonstrate the best evidence to be implemented in the local clinical practice. Nevertheless, all outcomes for this systematic review were defined *a priori*.

FINAL CONSIDERATIONS

Regarding the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection, there were no significant differences in the incidence of infected cases (positive RT-PCR), hospitalization, serious adverse events, and mortality between the groups during the follow-up period. In addition, the use of pre- or post-exposure prophylaxis with hydroxychloroquine increased the risk of adverse events by 12% (95% CI, 6-8%; NNH = 9) when compared with controls during the follow-up period. The quality of evidence varied from very low to moderate. Likewise, no significant differences in the number of hospitalizations, serious adverse events, and deaths were found between the hydroxychloroquine and control groups in patients with mild COVID-19, and the quality of evidence was high. The same result was found regarding the incidence of adverse events, but the quality of evidence was very low. Therefore, the use of hydroxychloroquine in the prophylaxis of SARS-CoV-2 infection or treatment of patients with mild COVID-19 is not recommended.

AUTHOR CONTRIBUTIONS

SET, HAB, AN, and WMB: study concept and design. WMB and SET: data collection. WMB and SET: statistical analyses and interpretation of data. WMB and SET: drafting of the manuscript. SET, HAB, AN, and WMB: critical review and approval of the final version.

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Consensus statement on thoracic radiology terminology in Portuguese used in Brazil and in Portugal

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ABSTRACT

Effective communication among members of medical teams is an important factor for early and appropriate diagnosis. The terminology used in radiology reports appears in this context as an important link between radiologists and other members of the medical team. Therefore, heterogeneity in the use of terms in reports is an important but little discussed issue. This article is the result of an extensive review of nomenclature in thoracic radiology, including for the first time terms used in X-rays, CT, and MRI, conducted by radiologists from Brazil and Portugal. The objective of this review of medical terminology was to create a standardized language for medical professionals and multidisciplinary teams.

Keywords: Tomography, X-ray computed; Radiography; Magnetic resonance imaging; Terminology as topic.

INTRODUCTION

The objective of medical terminology is to provide standardized language for medical professionals and multidisciplinary teams. This terminology allows effective multidisciplinary medical communication, faster sharing of data on and discussion of clinical cases, and data integration in patient clinical records. In addition, it should be noted that appropriate language can help reduce communication errors and inadequate documentation, which ensures that medical teams can analyze patient processes with greater speed and accuracy and, thus, provide faster diagnosis and treatment.[1,2]

In order to summarize recent evidence on imaging descriptors critically, 25 experts from Brazil and 3 experts from Portugal, all of whom are members of the Imaging Committee of the Brazilian Thoracic Association, were invited to develop the present consensus glossary. A panel of experts selected topics or questions related to the most significant changes in previously published concepts, including the terminology used in chest X-rays, CT, and MRI—terms that had not been addressed previously. Each invited expert was responsible for reviewing a topic or answering a question in this consensus glossary. In a second phase, 3 experts discussed and structured all texts submitted by the others, and, in a third phase, all experts reviewed and discussed the present recommendations. The present consensus statement brings an increase of more than 50% over previously published terminologies and includes terms used in chest X-rays, CT, and MRI.[2]

In thoracic radiology, the written radiology report is the most important and often the only instrument of communication between the radiologist and the requesting physician. The objective of the present consensus statement was to standardize the terminology used in reporting chest images in Portuguese used in Brazil (main

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subtitle) and used in Portugal. When the two languages have different terms for the same topic, the term in Portuguese used in Portugal is identified as [PP]. Since the original document was written in Portuguese, the terms in this translated English version are alphabetized by the names of their corresponding terms in Portuguese, which are shown in parentheses.

ACINUS (*ÁCINO*)

The acinus is a structural anatomical unit of the lung. It is distal to a terminal bronchiole and contains alveolar ducts and alveoli. The acinus participates in gas exchange and is 6-10 mm in diameter. One secondary lobule contains between 3 and 25 acini. Acini are only visible on imaging when they accumulate (pathological) material, appearing as poorly defined nodular opacities on X-ray, CT, and MRI.[1]

AIR TRAPPING OR GAS TRAPPING (*APRISIONAMENTO AÉREO OU APRISIONAMENTO GASOSO* [PP])

Air trapping is defined as retention of air (gas) in the distal airways and is visible on CT and MRI. It is best demonstrated in the expiratory phase and is seen as decreased attenuation of the lung parenchyma, showing lower-than-usual parenchymal density and lack of volume reduction (Figure 1).[1-3] It usually results from partial or complete airway obstruction or from focal abnormalities of lung compliance.[2]

ATELECTASIS OR COLLAPSE (*ATELECTASIA OU COLAPSO*)

Atelectasis is the term that describes reduced air volume in the affected lung. The most common mechanism of origin is airway obstruction with resorption of distal air. Atelectasis is characterized by volume loss, accompanied by opacity or increased attenuation, and displacement of fissures, bronchi, vessels, diaphragm, heart, or mediastinum (Figure 2). Passive atelectasis results from compression from pleural effusion or a mass. On imaging, atelectasis appears as an area of hyperdensity (CT scans) or hyperintense signal (MRI scans) in the lung, that shows lung volume reduction, air bronchogram, and loss of vessel definition. It can be identified on chest X-rays, CT, and MRI.

ROUNDED ATELECTASIS (*ATELECTASIA REDONDA*)

Rounded atelectasis refers to the presence of focal lung collapse that accompanies a variety of conditions.[4] It is typically associated with pleural disease, therefore being a relatively common finding in patients with asbestos exposure,[5] in whom it is usually associated with a previous exudative pleural effusion or is the result of adjacent pleural fibrosis or diffuse pleural thickening.[4-7] On axial imaging, rounded atelectasis appears as a round or oval mass that is located peripherally and abuts the pleural surface, which is usually thickened, with or without effusion. Rounded atelectasis is characteristically associated with a reduction in the volume of the involved lobe and with a curvilinear appearance of the vascular and bronchial structures adjacent to the lesion margins, forming the comet tail sign (Figure S1).[2,5] Because rounded atelectasis represents collapsed lung parenchyma, it can show intense enhancement after contrast agent injection on both CT and MRI, a useful feature in differentiating it from lung neoplasms, which usually do not show such intense contrast agent uptake on contrast-enhanced imaging studies.

PARENCHYMAL BAND (*BANDA PARENQUIMATOSA*)

A parenchymal band is defined as an elongated linear opacity, 1-3 mm thick and up to 5 cm long, that can be seen in patients with fibrosis or other causes of interstitial thickening.[1] These bands are usually peripheral and often abut the pleural surface, which may be thickened and retracted at the site of contact. They can represent contiguous thickened interlobular septa, peribronchovascular fibrosis, coarse scars, or atelectasis associated with lung or pleural fibrosis of

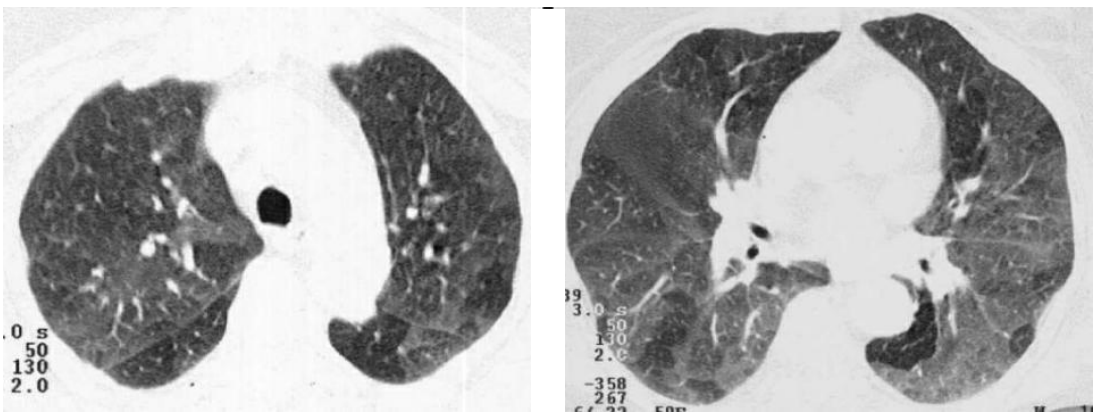

Figure 1. Axial CT scans with lung window settings acquired in the expiratory phase, revealing, in the posterior segments of the lower lobes, different parenchymal densities, with areas of decreased attenuation associated with air trapping due to small airway obstruction.

nonspecific cause (Figure S2).[5] Parenchymal bands are most often seen in patients with asbestos exposure and sarcoidosis.

FUNGUS BALL (*BOLA FÚNGICA*)

A fungus ball is defined pathologically as a mass of intertwined hyphae, usually of an *Aspergillus* species, colonizing a cavity containing mucus, fibrin, and cellular debris. It usually occurs in a cavity from prior fibrocavitary disease (e.g., tuberculosis or sarcoidosis), but it occasionally occurs in cysts, bullae, and bronchi. A fungus ball may move to a dependent location when the patient changes position and may show an air crescent sign (Figure 3). A fungus ball may appear as heterogeneous sponge-like attenuation and foci of calcification on CT and MRI. A synonym is aspergilloma.[8] See "Air crescent sign".

BULLA (*BOLHA*)

A bulla is defined pathologically as an airspace measuring more than 1 cm—and can be several centimeters—in diameter, demarcated by a thin wall that is no greater than 1 mm in thickness. A bulla is usually accompanied by emphysema and changes in the adjacent lung (See "Bullous emphysema"). On X-rays, CT, and MRI, a bulla appears as a rounded focal hyperlucency or area of hypoattenuation, 1 cm or more in diameter, bounded by a thin wall (Figure 4). Multiple bullae are frequent and are associated with pulmonary emphysema (centrilobular and paraseptal).[5]

BRONCHOCELE (*BRONCOCELE OU BRONCOCELO* [PP])

A bronchocele is defined pathologically as segmental bronchial dilatation, typically cylindrical and branching, that is completely or partially filled with secretions, usually mucoid ones. A bronchocele may be due either to obstructive disease, of congenital, tumoral, or foreign body etiology; or to non-obstructive disease, such as asthma, allergic bronchopulmonary aspergillosis, or cystic fibrosis. On X-rays, a bronchocele appears as an elongated opacity with branching morphology, being more evident in the central regions of the lung. On CT and MRI, a bronchocele appears as an elongated structure with cylindrical morphology, and can have a branching Y- or V-shaped appearance (Figure S3 and Figure 5). This appearance often resembles that of a "gloved finger". On CT, hypoattenuating lung parenchyma distal to the alteration, especially in cases of bronchial atresia due to reduced ventilation and perfusion, and increased attenuation within

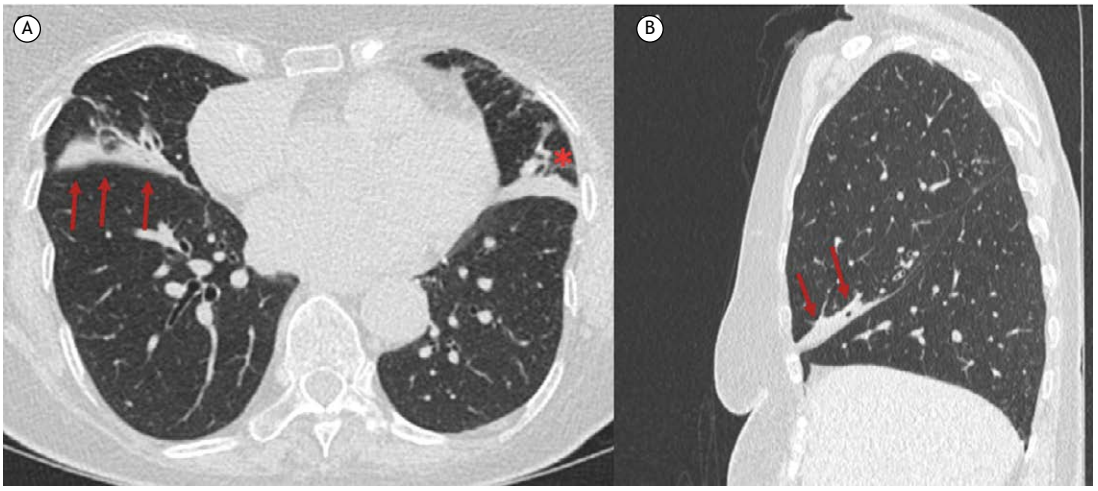

Figure 2. In A, an axial CT scan with lung window settings revealing atelectasis of the right middle lobe (arrows) and lingula (asterisk). In B, a coronal CT scan with lung window settings showing a slight displacement of the oblique fissure, bronchi, and adjacent vessels (arrows).

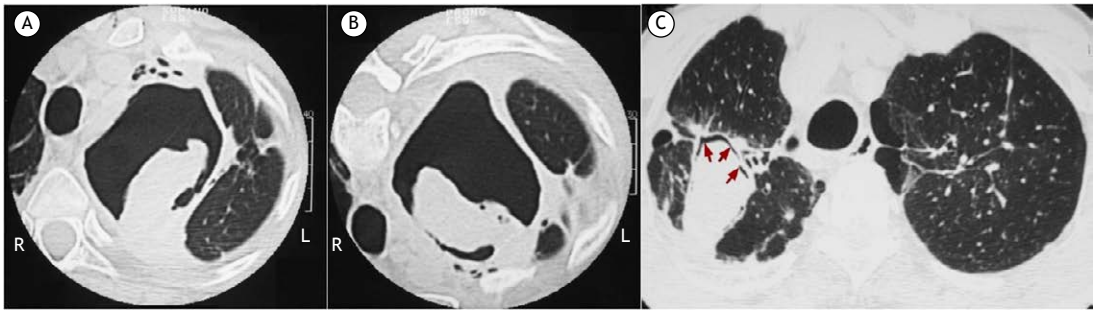

Figure 3. Axial CT scans with lung window settings acquired with the patient in the supine (A) and prone (B) positions, showing mobility of the fungus ball within a cavity in the left upper lobe. In C, an air crescent sign (arrows) within a cavity containing a fungus ball in the right upper lobe.

the bronchocele, which can be indicative of allergic bronchopulmonary aspergillosis, can be associated.[9]

AIR BRONCHOGRAM (*BRONCOGRAMA AÉREO*)

An air bronchogram is a branching air pattern within an area of increased attenuation of the lung parenchyma, reflecting air-filled bronchial structures in regions where there is no alveolar air, that is, regions of airspace filling (consolidation) or air absorption (atelectasis). On X-rays, an air bronchogram appears as a branching air pattern within an opacity. An X-ray finding of an air bronchogram indicates that the alteration is located in the lung parenchyma. On CT and MRI, an air bronchogram appears as an air-filled bronchial structure within a consolidation or area of atelectasis of the lung parenchyma (Figure 6). When associated with atelectasis, an air bronchogram may indicate that there is no obstruction of proximal airways. Air bronchograms can occasionally be observed in adenocarcinomas and pulmonary lymphomas.[10]

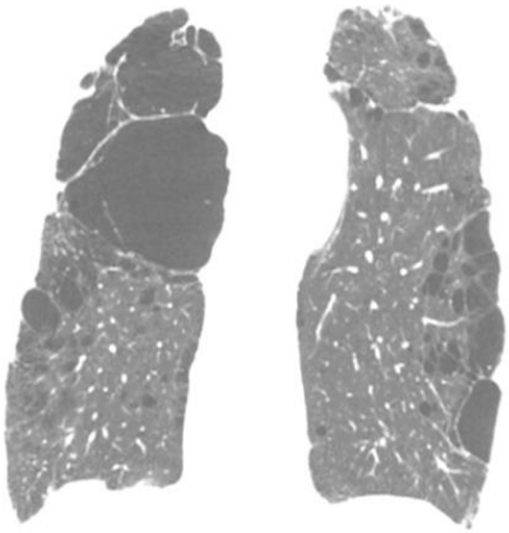

Figure 4. Coronal CT scans with lung window settings of a patient with centrilobular and paraseptal emphysema who has multiple bullae, the largest of which are located in the right lung apex.

BRONCHOLITH (*BRONCOLITO*)

A broncholith is defined pathologically as calcified or ossified material within the tracheobronchial tree. CT is superior to X-rays and MRI for diagnosis. The typical imaging appearance is of a focus of calcification adjacent to a bronchial wall or within a bronchus and with no soft tissue component, which distinguishes a broncholith from other lesions such as hamartomas or carcinoid tumors (Figure S4). Broncholiths are most common in the right upper and middle lobe bronchi, and can cause atelectasis, air trapping, and bronchiectasis because of the bronchial obstruction.[11]

BRONCHIECTASIS (*BRONQUIECTASIA*)

Bronchiectasis is defined pathologically as irreversible focal or diffuse bronchial dilatation, usually secondary to inflammation and/or infection, bronchial obstruction, or congenital abnormality. X-ray findings can be nonspecific and include linear and/or reticular opacities, bronchial wall thickening, or even the demonstration of the bronchial dilatation. The CT diagnosis is made when the internal diameter of the bronchus is greater than the diameter of the adjacent artery (signet-ring sign); when there is a lack of bronchial tapering, defined as no change in bronchial diameter over 2 cm, distal to the bronchial bifurcation (tram-track appearance), and when bronchi are visible within 1 cm of the pleural surface (Figure 7). MRI can detect the same findings of bronchial dilatation that are seen on CT, but with less accuracy. Bronchiectasis is morphologically classified as cylindrical, when there is uniform bronchial dilatation; varicose, when there

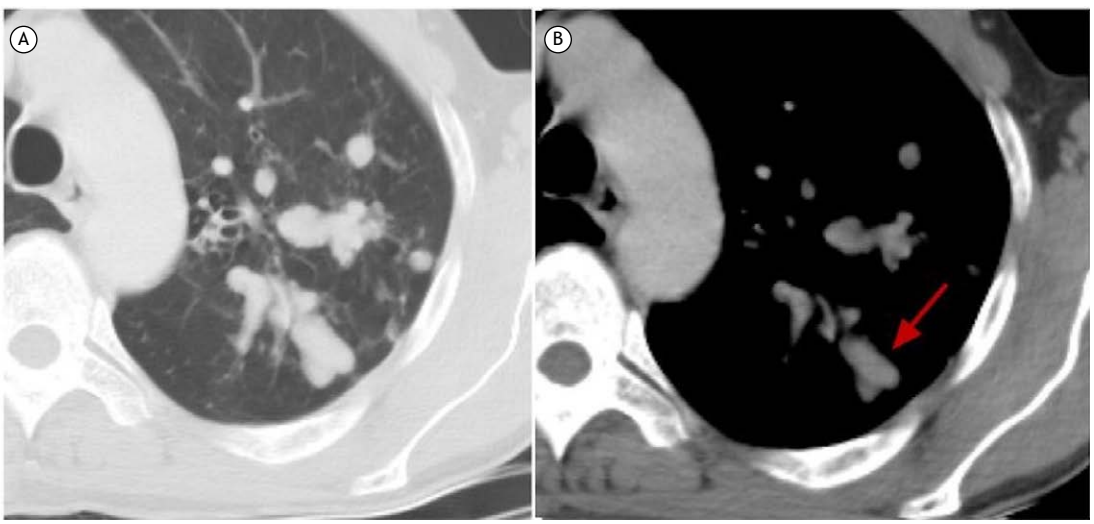

Figure 5. Axial CT scans of a patient with allergic bronchopulmonary aspergillosis (ABPA). In A, a CT scan with lung window settings showing bronchoceles. In B, a CT scan with mediastinal window settings showing increased attenuation (red arrow) within a bronchocele, suggesting the diagnosis of ABPA.

is irregular bronchial dilatation, with alternating areas of greater and smaller caliber; or cystic, when there is large focal dilatation, forming cysts.[12,13]

BRONCHIOLECTASIS (*BRONQUIOLECTASIA*)

Bronchiolectasis is defined pathologically as dilatation of bronchioles. It is caused by inflammatory activity (therefore potentially reversible) or, more frequently, fibrosis, in which case it is referred to as "traction bronchiolectasis". Bronchioles differ from bronchi in that they have no cartilage or glands in their walls. The largest bronchioles are between 0.8 and 1.0 mm in diameter, with diameters gradually becoming smaller toward the level of the respiratory bronchioles (the most distal ones, which have alveolar sacs on their walls), which are between 0.4 and 0.5 mm in diameter.[4,12,13] Normal bronchioles are not visible on HRCT, the resolution limit of which allows visualization of bronchi that are up to 2-3 mm in internal diameter.[14] When bronchioles are dilated and filled with secretions, they can be seen as centrilobular nodules or as a "tree-in-bud" pattern. Traction bronchiolectasis appears as small, cystic or tubular airspaces surrounded by fibrosis (Figure S5).[1,15,16]

Traction bronchiolectasis is difficult to characterize on X-rays, and, when this happens, it is usually observed in the periphery of the lung bases. On CT, traction bronchiectasis appears as bronchial dilatation that is

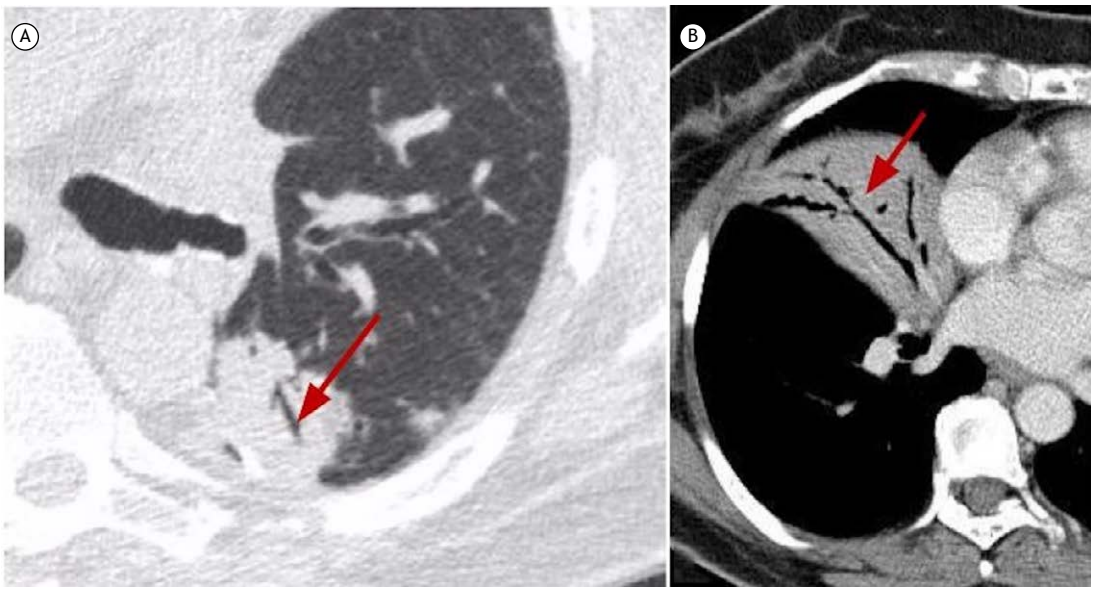

Figure 6. In A, an axial CT scan with lung window settings showing an air bronchogram (arrow) within a consolidation in the left lower lobe. In B, an axial CT scan with lung mediastinal window settings showing an air bronchogram (arrow) within a consolidation in the middle lobe.

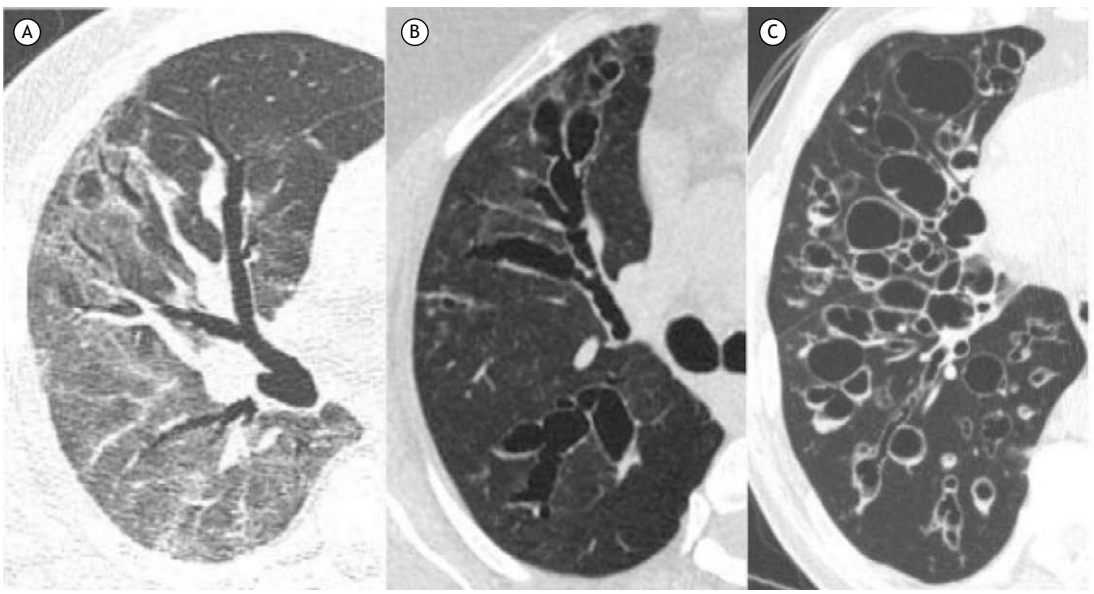

Figure 7. Axial CT scans with lung window settings showing cylindrical (A), varicose (B), and cystic (C) bronchiectasis.

tubular, cystic, or rounded in appearance, depending on the imaging axis. Traction bronchiolectasis is predominantly peripheral (juxtapleural), is smaller in internal diameter, and is associated with fibrosing interstitial lung changes (Figure S6). On MRI, traction bronchiolectasis is rarely visible and if so, it appears as a tubular structure of hypointense signal associated with areas of architectural distortion of the lung parenchyma.

CAVITY (*CAVIDADE*)

A cavity is defined pathologically as a gas-filled space, seen as a lucency or a low-attenuation area, within a mass, consolidation, or nodule.[1,2] On X-rays, CT, and MRI, a cavity is an airspace measuring more than 1 cm (and can be several centimeters) in diameter, demarcated by a thick wall > 2 mm in thickness (Figure S7).[15]

CYST (*CISTO OU QUISTO* [PP])

A cyst is described pathologically as a round circumscribed space that is surrounded by an epithelial or fibrous wall of variable thickness.[17,18] On chest X-rays, cysts are an infrequent and often inconclusive finding.[17,18] On CT, a cyst appears as a round area of low attenuation in the lung parenchyma, with a well-defined interface with normal lung (Figure 8).[17,18] Cyst walls are thin, being no greater than 2 mm in thickness. MRI is used for the study of mediastinal and thoracic non-air cystic lesions, playing an interesting role in their differential diagnosis and in determining hemorrhagic and fat components. Cysts usually contain air but occasionally contain fluid (e.g., bronchogenic cysts) or even solid material. Isolated pulmonary air cysts are common incidental findings and increase with age.[17,18] The presence of five or more pulmonary cysts is used as a criterion for the investigation of cystic lung diseases.[5] Cystic lung diseases usually present with multiple pulmonary cysts, often with increased lung volume, and include lymphangioleiomyomatosis, Langerhans cell histiocytosis, lymphocytic interstitial pneumonia, and Birt-Hogg-Dubé syndrome.[17,18] However, there are fibrosing lung diseases that produce cysts, such as honeycomb cysts. See "Honeycombing".

ARCHITECTURAL DISTORTION (*DISTORÇÃO ARQUITETURAL*)

Architectural distortion of the lung parenchyma is pathologically characterized by abnormal disorganized displacement of bronchi, vessels, fissures, or septa caused by diffuse or localized lung disease, particularly that associated with fibrosis and accompanied by volume loss.[1,2] The term "architectural distortion" can be used in X-rays, CT, and MRI reports to describe regions where there is extensive anatomical disorganization that hinders exact anatomical recognition of structures (Figure S8).

EMPHYSEMA (*ENFISEMA*)

Emphysema is characterized pathologically by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls and without obvious fibrosis. The additional histological criterion of "absence of obvious fibrosis" has been questioned because some degree of interstitial fibrosis may be present in emphysema secondary to smoking. The traditional pathological classification of emphysema is based on the microscopic localization of disease within the acinus or secondary lobule. The main types of emphysema include centriacinar or centrilobular emphysema, paraseptal or distal acinar emphysema, and panacinar or panlobular emphysema.[1,18-31] On CT, emphysema findings consist of areas of low attenuation, typically without visible walls.[2]

BULLOUS EMPHYSEMA (*ENFISEMA BOLHOSO*)

Bullous emphysema is not a specific histological entity but is rather the term for emphysema that is primarily characterized by the presence of a large bulla. Bullous emphysema is often associated with centrilobular and paraseptal emphysema (Figure S9).[18] It is called giant bullous emphysema when the bullae occupy at least one third of the hemithorax and are asymmetrically located in the upper lobes, ranging from 1 to more than 20 cm in diameter.[19] On CT, a bulla appears as a focal hypodense area, 1 cm or more in diameter, bounded by a thin wall that is no greater than 1 mm in thickness. It usually contains gas but may occasionally contain fluid.[1] Bullae that are less than 1 cm in diameter and are located within the visceral pleura or in the subpleural lung are called blebs. Apical blebs or vesicles are often responsible for primary spontaneous pneumothorax.[20]

CENTRILOBULAR/CENTRIACINAR EMPHYSEMA (*ENFISEMA CENTROLOBULAR/CENTROACINAR*)

This type of emphysema pathologically corresponds to selective enlargement of elements in the central portion of the acinus, particularly the respiratory bronchioles and associated alveoli. The process primarily affects the upper lobes and the upper portion of the lower lobes, being strongly associated with smoking and chronic bronchitis. Inflammatory changes in the small airways are common, with plugging, mural infiltration, and fibrosis, which cause stenosis and airflow blockage, as well as distortion and destruction of the central portion of the acinus.[21-23] CT findings include multiple small rounded centrilobular areas of decreased parenchymal attenuation, without visible walls (Figure 9). A thin opaque rim can be seen in the transition zone between the emphysematous area and normal lung, because of compression of the adjacent parenchyma by the dilated airspace. Centrilobular arteries can often be seen within hypodense areas.[22] X-ray and MRI findings of centrilobular emphysema are only indirect, demonstrating increased lung volume, and are not diagnostically reliable.

INTERSTITIAL EMPHYSEMA (*ENFISEMA INTERSTICIAL*)

Interstitial emphysema is characterized by air dissecting within the lung interstitium and can be spontaneous or traumatic. It is most commonly seen in neonates receiving mechanical ventilation.[24] Interstitial emphysema is rarely identified on chest X-rays and may appear as intrapulmonary or subpleural cyst-like formations, radiolucent streaks extending to the mediastinum, and perivascular halos from air collections.[22] On CT, it appears as unilateral or bilateral diffuse focal collections of air, which can simulate cysts or bullae, located in the interstitium adjacent to the interlobular vessels, bronchi, and septa (Figure S10).[25,26] X-ray and MRI findings of interstitial emphysema are nonspecific and are not diagnostically reliable.

PANACINAR OR PANLOBULAR EMPHYSEMA (*ENFISEMA PANACINAR OU PANLOBULAR*)

Panacinar emphysema is pathologically characterized by the enlargement of acinar airspaces, affecting the structures from the respiratory bronchioles to the alveoli. All components of the secondary lobule are affected more or less uniformly.[23] This type of emphysema is associated with alpha-1 antitrypsin deficiency. Panacinar emphysema can be found in smokers, associated with centrilobular emphysema, and in intravenous drug users (chronic effect). In addition, it can be found around bronchoceles in patients with bronchial atresia. Chest X-rays may be normal in earlier disease stages. In more advanced stages, there is vascular distortion and rarefaction. Other findings include flattening of the diaphragm, increased anteroposterior chest diameter, and increased retrosternal space.[27] On CT, the lesions are homogeneously distributed, predominating in the lower lobes, and are characterized by a diffuse decrease in attenuation of the lung parenchyma with vascular rarefaction in the affected areas (Figure S11). Bronchiectasis may also be found. It may be difficult to differentiate between areas of normal lung parenchyma and areas of emphysema. Panacinar emphysema is indistinguishable from (constrictive) obliterative bronchiolitis.[28] MRI findings of panacinar

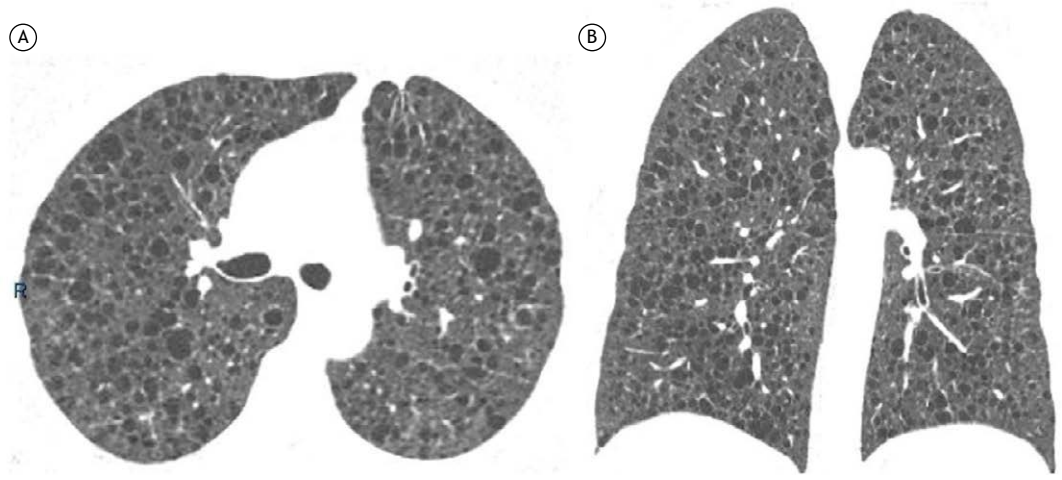

Figure 8. Axial (A) and coronal (B) CT scans with lung window settings revealing multiple pulmonary cysts in a female patient with lymphangioleiomyomatosis.

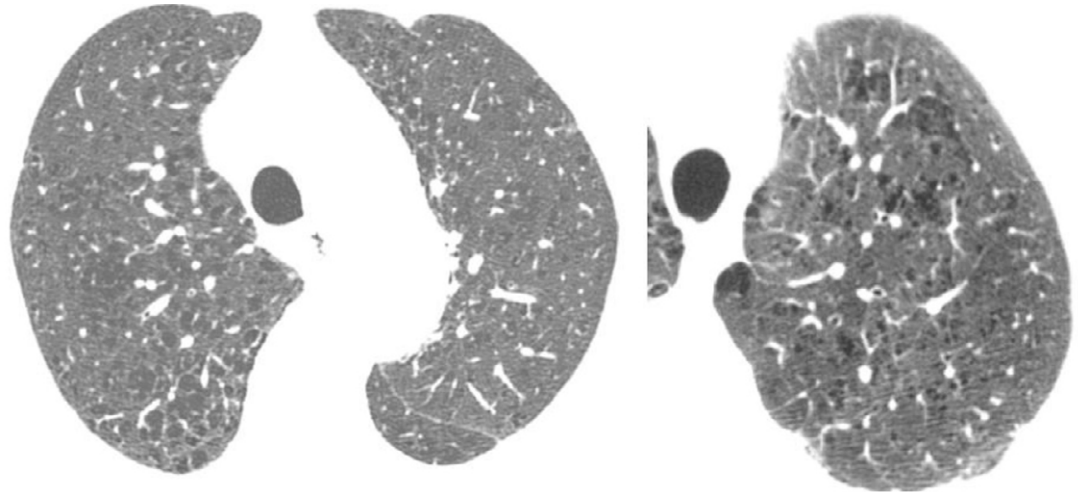

Figure 9. Axial CT scans with lung window settings revealing centrilobular emphysema in the upper lobes in a smoker.

emphysema are only indirect, demonstrating increased lung volume, and are not diagnostically reliable.

PARASEPTAL OR DISTAL ACINAR EMPHYSEMA (*ENFISEMA PARASSEPTAL OU ACINAR DISTAL*)

This type of emphysema is pathologically characterized by permanent enlargement of the distal acinus, accompanied by destruction of alveolar ducts and sacs and with dilated alveoli in a subpleural location adjacent to the interlobular septa.[29] On chest X-rays, less severe forms of paraseptal emphysema are difficult to detect. Radiolucent thin-walled structures may be seen in the lung periphery.[27] On CT, subpleural and peribronchovascular cystic formations are seen, possibly separated by intact interlobular septa. The anterior and posterior portions of the upper lobes and the posterior portions of the lower lobes are most often affected. Bullae may be associated with this form of emphysema (Figure S12). The use of minimum-intensity projection reconstruction facilitates lesion detection.[30] MRI findings of paraseptal emphysema are nonspecific and are not diagnostically reliable.

AIRSPACES (*ESPAÇOS AÉREOS*)

The term "airspace" is a generic description that refers to the aerated portion of the lungs where there is gas exchange, that is, the respiratory bronchioles, alveolar ducts, and alveoli. This term excludes the purely conducting portion of the airways, from the trachea to the terminal bronchioles. Airspaces represent most of the normal lung. This term is usually used in conjunction with airspace-occupying diseases in which lung gas content is replaced by pathological products, either cells or fluid. In various lung diseases, the airspaces are occupied uniformly or areas of aerated lung are preserved within the lesion.[2,32] On X-rays, the presence of air bronchograms may indicate the filling of the airspaces around the bronchi. On CT, lesions such as consolidations, masses, and nodules affect various lung compartments, including airspaces. Mostly, the term "airspace" is used when referring to airspace filling with pathological products or when there is aerated lung within those lesions (Figure S13). It is important to distinguish an airspace from a cavity, in which there is no gas content with no lung parenchyma.[1,2,32] See "Cavity".

INTERLOBULAR SEPTAL THICKENING (*ESPESSAMENTO DE SEPTOS INTERLOBULARES*)

Interlobular septa are anatomically part of the peripheral interstitial framework of the lung, surround the secondary pulmonary lobule, and are composed of connective tissue, veins, and lymphatics. Normal interlobular septa are usually not visible on imaging. When thickened, they appear on X-rays as peripheral, thin linear opacities perpendicular to the pleural surface and are best visualized in the periphery of the lung bases. They are also called Kerley B lines.[1,2,32] On CT and MRI, they appear as peripheral/subpleural linear opacities perpendicular to the pleural surface, approximately 1.0-2.5 cm apart from each other. When the septa of several adjacent secondary pulmonary lobules are thickened, they may take on the appearance of polygonal arcades (Figure 10).[4,18,30]

HONEYCOMBING (*FAVEOLAMENTO*)

Honeycombing is pathologically represented by acini dilated by fibrosis and forming cystic structures resulting from the collapse of neighboring acini. The cysts have thick, fibrous walls and are lined by metaplastic bronchiolar epithelium. On CT, honeycombing is seen as a cluster of cystic structures associated with reduced lung volume, typically has dimensions on the order of subcentimeters, and is usually subpleural. On MRI, the findings are similar, but the detection accuracy of MRI is lower than that of CT.[18] Although honeycombing is represented by multiple layers of cysts in most cases, a cluster of two to three cysts together with other findings of fibrosis can be characterized as honeycombing.[4,18] Honeycombing represents the late stage of various lung diseases, with complete loss of lung architecture, such as usual interstitial pneumonia and sarcoidosis (Figure S14).[4,18]

FISSURE (*FISSURA*)

A fissure is anatomically defined as the infolding of visceral pleura that lines the outer surface of the lung and separates one lobe (or part of a lobe) from another. Each interlobar fissure is formed by the apposition of two layers of visceral pleura. In general, we can identify the major (or oblique) fissures, which separate the lower lobes from the other lobes, and the minor (or horizontal) fissure, which separates the middle lobe from the right upper lobe. Supernumerary fissures usually separate segments rather than lobes. Fissures may be incomplete. On imaging, fissures appear as linear opacities that correspond in position to the anatomic separation of pulmonary lobes or segments.[1,33]

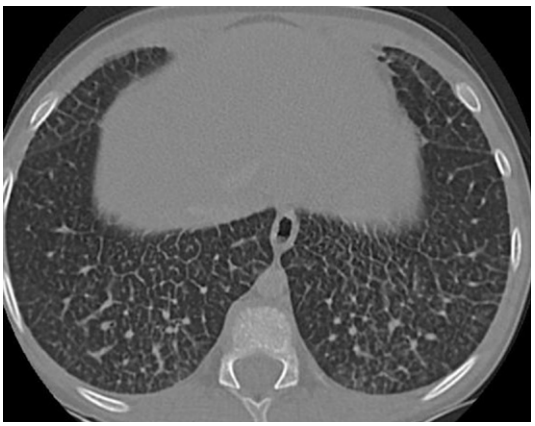

Figure 10. A CT scan with lung window settings revealing diffuse interlobular septal thickening, forming polygonal arcades.

INFILTRATE (*INFILTRADO*)

Infiltrate is considered an imprecise and nonspecific term often used to describe a region of pulmonary opacification, identified on X-rays, MRI, or CT, that is caused by airway or interstitial disease. Because infiltrate means different things to different people, it is considered a controversial term and is not recommended. We suggest that it be replaced by the term "opacity".[34]

INTERFACE (*INTERFACE*)

Interface is an anatomical term to describe the boundary between two structures or tissues of different densities. When two thoracic structures of different radiological densities are juxtaposed, their boundaries are clearly defined. In imaging, this term is used only in HRCT studies of interstitial lung diseases. The interface sign is characterized by the presence of irregular interfaces between the lung and bronchi, vessels, and visceral pleura, being suggestive of interstitial thickening, usually associated with other changes, which together allow the diagnosis.[33,35,36]

INTERSTITIUM (*INTERSTÍCIO*)

Interstitium is an anatomical term to describe the network of connective tissue that extends throughout the lungs and serves for their support. It comprises the following subdivisions: (a) axial (or bronchovascular) interstitium, which surrounds the bronchi, arteries, and veins from the hilum to the level of the respiratory bronchiole; (b) peripheral interstitium, which is the connective tissue contiguous with the pleural (subpleural) surfaces and interlobular septa; and (c) intralobular interstitium (also called acinar or parenchymal interstitium), which is a network of fine fibers interposed between the alveolar walls and the alveolar septal walls.[1,36] The normal interstitium is not visible on imaging.

SUBPLEURAL CURVILINEAR LINE (*LINHA CURVILÍNEA SUBPLEURAL*)

A subpleural curvilinear line represents passive physiological compression of the dependent portion of the lung (e.g., of the posterior surface of the lung in patients in the supine position), which resolves after positional change. It may also be encountered in patients with pulmonary edema or fibrosis (Figure S15).[1] On CT and MRI, it appears as a thin curvilinear opacity, 1-3 mm in thickness, usually lying less than 1 cm from and parallel to the pleural surface.

SECONDARY PULMONARY LOBULE (*LÓBULO PULMONAR SECUNDÁRIO*)

Secondary pulmonary lobule is an anatomical term to describe the smallest unit of lung surrounded by connective tissue septa called interlobular septa. Each secondary pulmonary lobule is polyhedral in shape, measures 1.0-2.5 cm in diameter, and contains a variable number of acini. The core of the lobule is composed of bronchioles and their accompanying pulmonary arterioles, lymphatics, and surrounding interstitium. Interlobular septa contain small pulmonary veins and lymphatics (Figure 10).[37,38] Normal interlobular septa are not visible on imaging.

MASS (*MASSA*)

Mass is an imaging term to describe any expansile pulmonary, pleural, mediastinal, or chest wall lesion of soft tissue density, greater than 3 cm in diameter, and with at least partially defined contours, without regard to contour characteristics or content heterogeneity.[1,39] The term can be used in X-rays, CT, and MRI. Pulmonary masses (Figure 11) are often associated with primary or metastatic neoplastic lesions; however, they may also represent inflammatory lesions, such as pseudotumors and organizing pneumonia (OP), or infectious lesions, such as tuberculomas and cryptococcomas.[40] Mediastinal masses can be classified by location in the mediastinum as anterior mediastinal (prevascular), middle mediastinal (visceral), or posterior mediastinal (paravertebral) masses to increase accuracy in differential diagnosis.[41]

MYCETOMA (*MICETOMA*)

Mycetomas characteristically represent a group of chronic subcutaneous infections caused by traumatic skin inoculation with material contaminated with actinomycetes, especially species of the genera *Nocardia, Streptomyces*, and *Actinomadura*, or true fungi (eumycetes), including the genera *Acremonium, Fusarium, Leptosphaeria*, and *Madurella*, resulting in actinomycetoma and eumycetoma, respectively.[42,43] Mycetomas tend to invade adjacent tissues, forming nodules or masses with cavities and fistulous tracts, with purulent discharge containing grains composed of masses of hyphae and filaments. In most cases, they are located in the legs and can lead to deformities and fractures. Pulmonary and pleural involvement is rare.[42] When the lung is affected, the appearance is of consolidation with necrosis, and pleural effusion may be seen.[43] Mycetomas usually affect farm workers and are endemic in Latin America, India, and Africa.[42-46] Mycetomas do not arise from colonization of preexisting pulmonary cavities; therefore, the use of the term "mycetoma" as a synonym for "fungus ball" should be avoided. See "Fungus ball".

NODULE (*NÓDULO*)

A nodule is defined as a focal opacity that is roughly rounded, or at least partially circumscribed; has soft tissue, fat tissue, or calcified tissue density; and measures up to 3 cm in diameter (opacities greater than 3 cm should be referred to as a "mass"; Figure 12).[1,41] The term "nodule" can be used in X-rays, CT, and MRI. The term "small nodule" is suggested

for opacities up to 10 mm in mean diameter (average of the two largest diameters perpendicular to each other, preferably in the axial plane) or in diameter in another orthogonal plane if the opacities are larger in the longitudinal direction. Nodules larger than 10 mm should be measured at their largest and smallest orthogonal diameters. Nodules smaller than 3 mm require no formal measurement and can be termed micronodules.[47,48] Nodules can be divided into solid nodules, when they completely obscure the contours of vessels and bronchial walls (Figure 12); pure ground-glass nodules, when they do not obscure the vascular margins or bronchial walls (Figure 12); and part-solid nodules, when there are areas of soft-tissue attenuation and areas of ground-glass attenuation (Figure 12).[47] In addition, nodules should be described according to their margins, morphology, and location. Perifissural nodules with elongated or polygonal morphology, for example, indicate benignity (pulmonary lymph nodes).[48] Multiple nodules should be classified according to their distribution (random nodular pattern, perilymphatic nodular pattern, or centrilobular nodular pattern, the latter with or without a tree-in-bud pattern). See "Mass", "Nodular pattern", "Miliary pattern", and "Tree-in-bud pattern".

OLIGEMIA (*OLIGOEMIA*)

Oligemia is a term that represents a focal, regional, or generalized reduction in pulmonary blood volume. Oligemia is demonstrated on CT and MRI but rarely on X-rays. It appears as a regional or widespread decrease in the caliber and number of pulmonary vessels, which is indicative of less than normal blood flow (Figure S16).[1,2] Occasionally, areas of increased lung perfusion can simulate the appearance of ground-glass opacities, and, in differential diagnosis, it should be noted that there is a reduction in the number and caliber of the vessels in the regions of increased pulmonary lucency (Figure S17).[49-51]

OPACITY (*OPACIDADE*)

Opacity is a generic term to describe any area that, because of its greater density, is at least partially distinguishable from the surrounding or superimposed structures. In chest X-ray studies, this term does not indicate the pathologic nature, size, or specific location of the abnormality. Opacities may either have a pulmonary, pleural, or chest wall origin or be caused by something external to the patient. On CT, pulmonary opacities may completely obscure the vascular structures and bronchial walls (as occurs in consolidation, solid nodules, and masses) or may appear as ground-glass attenuation (in which case the vascular structures and bronchial walls remain visible).[1,2] The term "opacity" is not recommended for use in MRI. This term has some derivatives that merit discussion. See "Consolidation", "Ground-glass opacity", and "Mass".

GROUND-GLASS OPACITY (*OPACIDADE EM VIDRO FOSCO OU DESPOLIDO* [PP])

Ground-glass opacity is defined as an area of increased lung density (opacity) with attenuation that does not obscure underlying vascular structures.

On chest X-rays, ground-glass opacity appears as an area of hazy, low density, within which margins of pulmonary vessels may be indistinct. The considerable overlapping of structures on X-rays may lead to an incorrect interpretation of this finding, and the use of the term "ground-glass opacity" should therefore be avoided. On CT, ground-glass opacity appears as increased density of the lung parenchyma, with preservation of vascular and bronchial margins (Figure 13). It can represent interstitial thickening, partial filling of airspaces (with fluid, cells, and/or fibrosis), partial collapse of alveoli, increased capillary blood volume, or a combination of these mechanisms.[52,53]

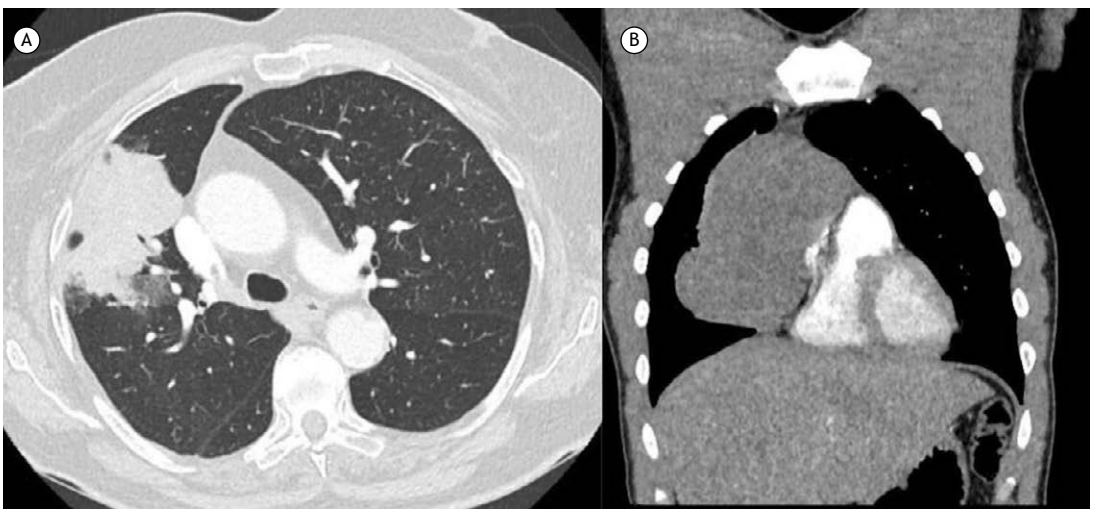

Figure 11. Axial CT scans with lung window settings. In A, a mass with lobulated contours in the anterior segment of the upper lobe of the right lung in a patient with lung adenocarcinoma. In B, an anterior mediastinal (prevascular) mass, with soft-tissue attenuation, in a patient with mediastinal seminoma.

Ground-glass opacity is less dense than and should be distinguished from consolidation, in which vessels are not identifiable within the affected area of lung (see "Consolidation"). Ground-glass opacity superimposed with intralobular lines and thickened interlobular septa results in a crazy-paving pattern (see "Crazy paving"). Ground-glass opacity with rounded/nodular morphology can be termed a subsolid nodule, which includes pure ground-glass nodules, that is, nonsolid nodules (Figure 13), or semisolid nodules, which contain soft-tissue density components.

On MRI, ground-glass opacity appears as an area of increased intensity on T2-weighted images, which is commonly observed in pathological processes, and this MRI finding highly correlates with CT findings of ground-glass opacity.[1]

LINEAR OPACITY (*OPACIDADE LINEAR*)

On X-rays and CT, linear opacity appears as a thin elongated structure of greater density than the lung parenchyma (causing greater attenuation of the X-ray beam), with a number of etiologies. It is recommended whenever possible to use terms that are more specific, such as "parenchymal band", "linear atelectasis", or "interlobular septal thickening" (Figure S18).[2]

PARENCHYMAL OPACITY OR PARENCHYMAL OPACIFICATION (*OPACIDADE PARENQUIMATOSA OU OPACIFICAÇÃO PARENQUIMATOSA*)

On X-rays and CT, this type of opacity is characterized as any area of greater attenuation of the X-ray beam relative to the lung parenchyma. Increased attenuation of the lung parenchyma may or may not obscure the margins of vessels and bronchi (Figure 14). The term "consolidation" indicates loss of definition of the margins of vessels and bronchi (except for air bronchograms) within the opacity, whereas the term "ground-glass opacity" indicates a smaller increase in parenchymal attenuation, in which the definition of underlying structures is preserved.[1,2,54,55]

DEPENDENT OPACITY (*OPACIDADE PENDENTE*)

On X-rays and CT, dependent opacity appears as increased density (greater attenuation of the X-ray beam) of the lung parenchyma in posterior subpleural regions (in the supine position) or anterior subpleural regions (in the prone position), representing positional atelectasis. It disappears with positional changes (Figure S18).[1,2]

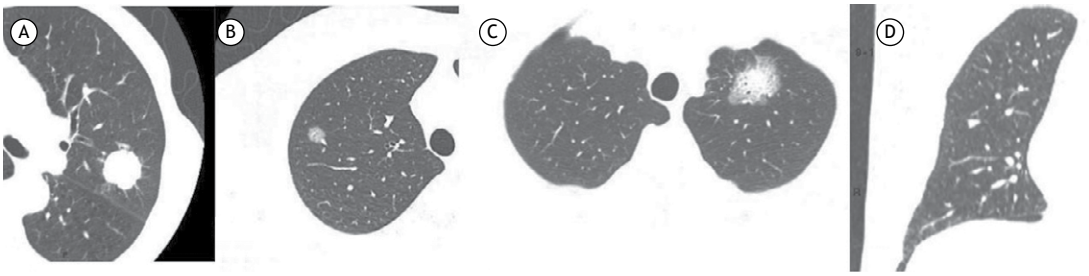

Figure 12. Axial CT scans with lung window settings. In A, a solid nodule with lobulated and spiculated margins in the apicoposterior segment of the upper lobe of the left lung. In B, a pure ground-glass nodule in the apical segment of the upper lobe of the right lung. In C, a mixed (part-solid, part ground-glass) nodule in the upper lobe of the left lung. In D, a perifissural nodule, polygonal in morphology, adjacent to the horizontal fissure of the right lung (pulmonary lymph node).

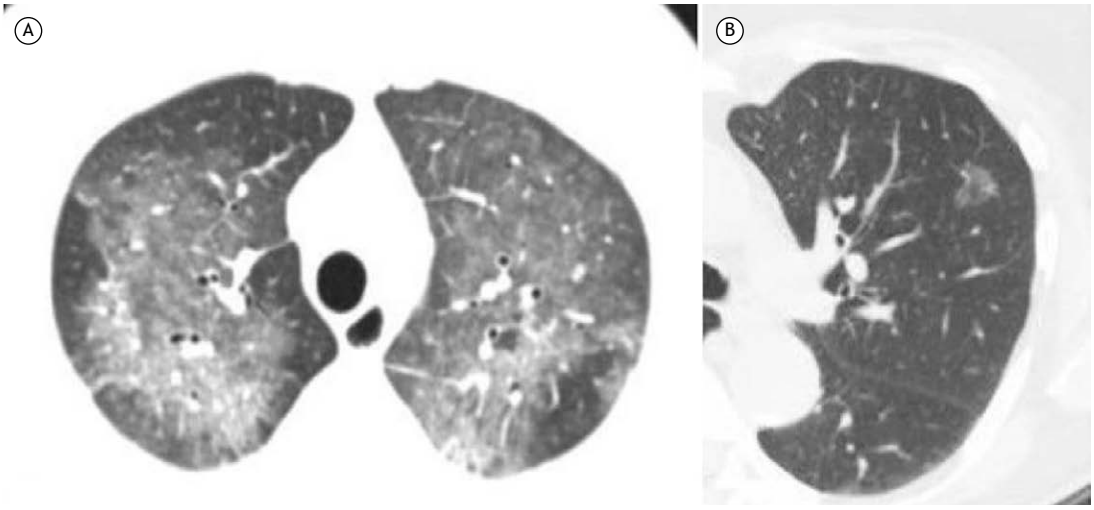

Figure 13. Axial CT scans with lung window settings demonstrating ground-glass opacities and predominant central distribution in both lungs in a patient with pulmonary edema (A) and revealing a ground-glass (subsolid) nodule that was diagnosed as lepidic growth adenocarcinoma (B).

CRAZY PAVING (PAVIMENTAÇÃO EM MOSAICO)

Crazy paving is a CT-specific term that describes a mixed pattern consisting of thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacity. It occurs in conditions involving the interstitium and the airspace. It is encountered in various diseases such as alveolar proteinosis, alveolar hemorrhage, ARDS, or infections, such as *Pneumocystis carinii* infection or the recent SARS-CoV-2 infection (Figure S19).[56,57]

TREE-IN-BUD PATTERN (*PADRÃO DE ÁRVORE EM BROTAMENTO OU EM BOTÃO* [PP])

The term "tree-in-bud pattern" can be used in X-rays, CT, and MRI, and is defined as centrilobular branching opacities/nodules, with small nodularities at the extremities, that resemble a budding tree (Figure 15). This pattern results from the filling of centrilobular branching structures, whether the centrilobular bronchiole or artery. It reflects a broad spectrum of endo- and perilobular changes, including inflammation and exudation.[1,58]

In most cases, this pattern represents dilated bronchioles filled with pathological material, although it may also be associated with infiltration of the peribronchial connective tissue in the centrilobular vasculature or, occasionally, with dilatation or filling (e.g., intravascular metastases) of the centrilobular arteries.[58]

MILIARY PATTERN (*PADRÃO MILIAR*)

A miliary pattern is an imaging finding on X-rays, CT, and MRI. It consists of nodules < 3 mm (micronodules) that are randomly and diffusely distributed and are uniform among themselves.[59] It is often a manifestation of hematogenous spread of tuberculosis and metastatic disease (Figure S20).[1,2,60]

MOSAIC PERFUSION PATTERN (*PADRÃO DE PERFUSÃO EM MOSAICO*)

A mosaic perfusion pattern is a CT finding defined as a patchwork of areas of different attenuation. It results from small airways obliteration or occlusive vascular disease, both of which producing areas of oligemia (decreased attenuation) that are interspersed with areas of normally ventilated and perfused lung. In cases of obliterative small airways disease, expiratory CT enhances the parenchymal foci that are hypodense (decreased attenuation) because of the air-trapping component.[1,2,61] The use of the term "mosaic attenuation" is no longer recommended because it increases the chances of misinterpretation

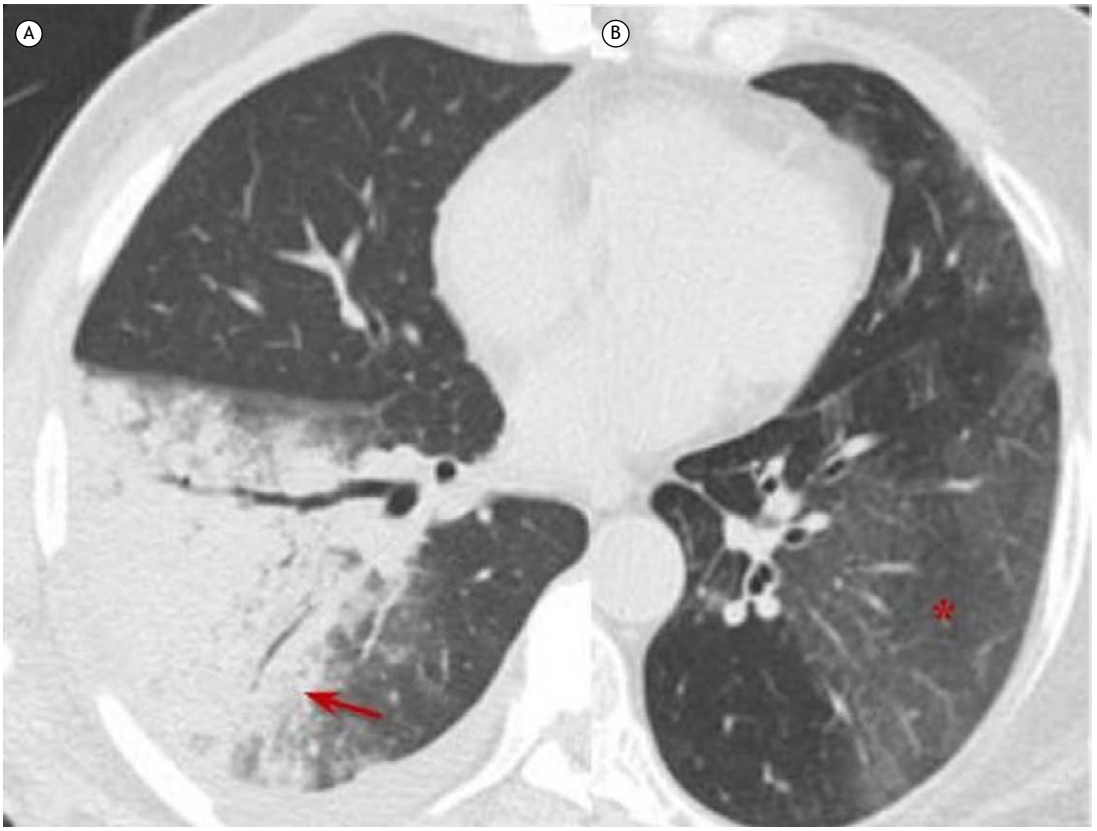

Figure 14. Axial CT scans with lung window settings showing parenchymal opacities that obliterate the contours of vessels and bronchi in the right lower lobe (arrow), indicating consolidation, together with an air bronchogram in the opacity (A), and parenchymal opacities preserving the contours of vessels and bronchi in the left lower lobe (asterisk), indicating ground-glass opacities (B).

regarding the term "mosaic perfusion". The term "non-homogeneous ground-glass opacity" should be used instead of mosaic attenuation.

NODULAR PATTERN (*PADRÃO NODULAR*)

A nodular pattern refers to the presence of multiple round soft-tissue density pulmonary opacities less than 3 cm in diameter. This pattern can be demonstrated on X-rays, CT, and MRI. Small nodules (or micronodules) are those that are less than 1 cm in diameter. On the basis of their distribution in the lung parenchyma, they can be classified as perilymphatic, random, or centrilobular. A centrilobular distribution is characterized by nodules that occupy the central portion of the secondary pulmonary lobule and are within a few millimeters of the pleural surface and fissures but do not touch them. In general, this type of distribution is associated with bronchiolar diseases, arteriolar diseases, or peribronchovascular bundle diseases.[60] The nodular pattern is primarily seen in silicosis, hypersensitivity pneumonitis, and some forms of bronchiolitis. In most cases, the nodules found in hypersensitivity pneumonitis and bronchiolitis exhibit ground-glass attenuation.[61,62]

PERILOBULAR PATTERN—PERILOBULAR OPACITIES, PERILOBULAR THICKENING (*PADRÃO PERILOBULAR — OPACIDADES PERILOBULARES, ESPESSAMENTO PERILOBULAR*)

A perilobular pattern represents involvement of the periphery of the secondary pulmonary lobule (i.e., the perilobular region) by variable histopathological substrates.[63,64] On CT and MRI, it is seen as linear/curvilinear opacities surrounding interlobular septa, with the former being larger and less defined than the latter, and usually producing an appearance resembling a polygon or arch (Figure S21).[63-66] The differential diagnosis includes OP, a pattern that is observed with differing frequency (22-57%) and represents collection of organizing inflammatory material in the periphery of the pulmonary lobule, with or without septal thickening.[63-65] In OP, the perilobular pattern is often associated with other typical findings, such as consolidations, rather than being an isolated finding.[66]

RETICULAR PATTERN (*PADRÃO RETICULAR*)

A reticular pattern represents involvement of the pulmonary interstitia by variable histopathological substrates. On X-rays, it appears as linear structures that are sometimes intertwined and are more easily seen in the periphery of the lung fields. On CT and MRI, it usually corresponds to inter- or intralobular septal thickening, but it can sometimes represent cysts whose walls appear as lines on X-rays (Figure S22). It is often, but not invariably, associated with fibrosing diseases, in which case signs of volume loss of the lung parenchyma are also observed.[1,67]

PSEUDOPLAQUE (*PSEUDOPLACA*)

A pseudoplaque is an opacity contiguous with the visceral pleura, formed by coalescent small nodules.

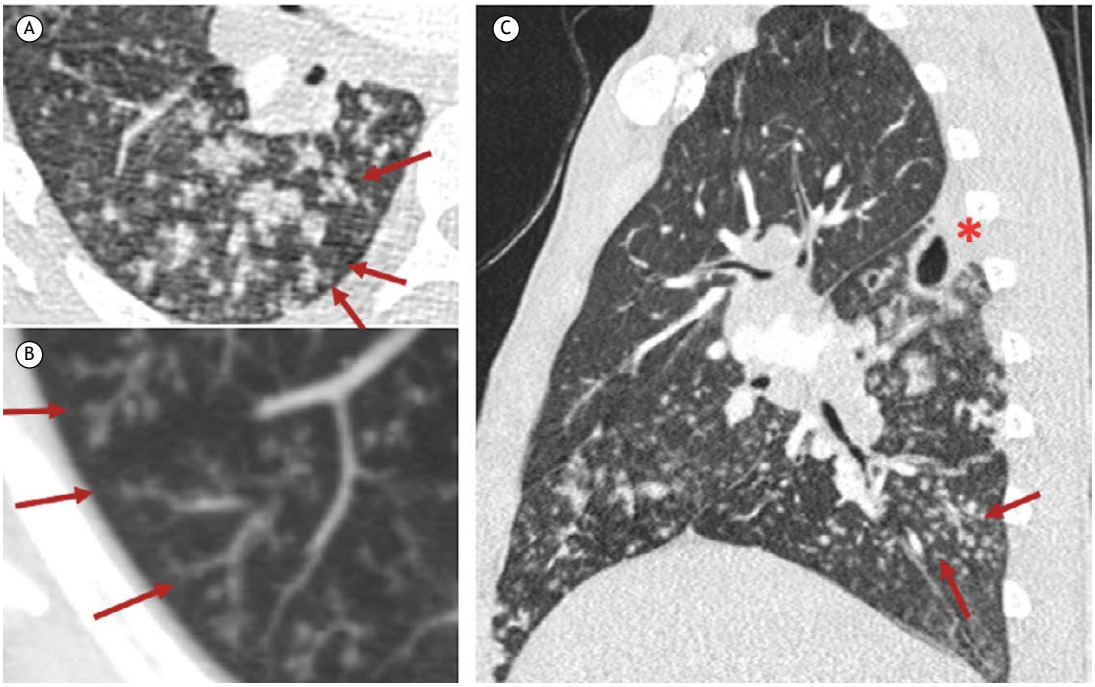

Figure 15. CT scans with lung window settings of a male patient with pulmonary tuberculosis. In A, an axial CT scan showing multiple centrilobular opacities with small nodules and branching structures (arrows). In B, maximum-intensity projection reconstruction demonstrating opacified structures that reflect endobronchial filling of the distal bronchioles (arrows). In C, a sagittal CT scan showing, in addition to centrilobular nodules and a tree-in-bud pattern (arrows), the presence of a cavity in the upper segment of the right lower lobe, which is a characteristic location for cavitation (asterisk) in pulmonary tuberculosis.

It simulates the appearance of a pleural plaque. This entity can be identified on CT and MRI and is encountered most commonly in sarcoidosis, silicosis, and coal workers' pneumoconiosis.[1]

PLEURAL PLAQUE

A pleural plaque pathologically represents an elongated area of dense connective tissue on the pleural surface that appears as focal thickening on X-rays or more commonly on CT and MRI (Figure S23).[1,68-70] It may be an incidental finding. However, when there are multiple pleural plaques, a differential diagnosis between asbestos exposure and sequelae of empyema/tuberculosis (usually unilateral and extensive) is necessary. Sometimes, pleural plaques are calcified, in which case they are more easily detected on X-rays as vertical linear structures parallel to the chest wall.

PNEUMATOCELE (*PNEUMATOCELE*)

A pneumatocele can be identified on X-rays, CT, and MRI, and is defined as a thin-walled (< 1 mm) and gas-filled rounded cystic structure that changes size within a short period of time (Figure S24). It results from a check-valve mechanism of airway obstruction. Occasionally, it may contain fluid. A pneumatocele usually resolves spontaneously. It is most often seen in children, in association with infectious processes, especially in children with pneumonia caused by *Staphylococcus* sp. and in immunocompromised children with pneumonia caused by *Pneumocystis jirovecii*.[71] It can also be seen in preterm neonates with respiratory distress.[72]

PSEUDOCAVITY (*PSEUDOCAVIDADE*)

Pseudocavity is a term used in CT to describe a round or oval, low-attenuation cystic area, usually < 1 cm in diameter, in lung nodules, masses, or areas of consolidation. A pseudocavity is sometimes difficult to differentiate from a pulmonary cavity. Pseudocavities can represent dilated or normal bronchi, areas of emphysema within a lesion, or areas of preserved lung parenchyma (Figures S25 and S26). The presence of a pseudocavity in nodules is often associated with adenocarcinoma and can be seen in pneumonia with necrotizing consolidation (Figure S26).[71-73]

PNEUMOMEDIASTINUM (*PNEUMOMEDIASTINO*)

Pneumomediastinum is an imaging finding defined as the presence of air/gas in the mediastinum. Air or gas can reach the mediastinal spaces as a result of a sudden increase in intra-alveolar pressure, with consequent rupture of alveoli and tracking of gas along the peribronchovascular interstitium to the hilum and into the mediastinum. CT is the gold standard for diagnosis, which can also be made by X-rays (Figure S27). MRI is not used. Pneumomediastinum may also be due to rupture of hollow organs, such as the esophagus, trachea, bronchi, or even the neck or abdominal cavity. Pneumomediastinum is often associated with pneumothorax.[74]

PNEUMOTHORAX (*PNEUMOTÓRAX*)

Pneumothorax refers to the presence of air in the pleural space. It is usually classified as spontaneous, traumatic, diagnostic/iatrogenic, or tension, according to its etiology. It can be identified on X-rays, CT, and MRI (Figure S28). When its dimensions are significant (> 2 cm between the pleural surface and the pulmonary contour), pleural tube placement is indicated.[1,2,74] In most cases, pneumothorax is caused by trauma such as rib fracture or penetrating chest trauma. Hypertensive pneumothorax is a medical emergency, because the air in the pleural cavity is under pressure, which causes associated vascular collapse and decreased venous return to the left atrium. Iatrogenic pneumothorax often results from thoracic procedures such as lung biopsy, central venous catheter insertion, or thoracic surgery.[75]

TARGET SIGN (*SINAL DO ALVO*)

The target sign consists of a peripheral ring-shaped opacity in conjunction with a central nodular ground-glass opacity. The target sign can be demonstrated on CT and MRI. This finding was first described in association with SARS-CoV-2 pneumonia (Figure S29).[76] However, recent studies indicate that the etiopathogenesis of the target sign is similar to that of the reversed halo sign as a radiological sign of OP.[77]

ARCH SIGN—PERILOBULAR SEPTAL THICKENING (*SINAL DA ARCADA — ESPESSAMENTO SEPTAL PERILOBULAR*)

The arch sign consists of an arch-shaped linear opacity with a perilobular distribution, around the secondary pulmonary lobule. This finding, like the target sign and the reversed halo sign, indicates OP (Figure S30).[77,78] The arch sign can be demonstrated on CT and MRI.

SIGNET RING SIGN (*SINAL DO ANEL DE SINETE*)

The signet ring sign is composed of a ring-shaped opacity, representing a dilated bronchus in axial section, and a smaller adjacent opacity, representing its pulmonary artery, with the combination resembling a signet (or pearl) ring. This sign is a diagnostic CT feature of bronchiectasis (Figure S31). The signet ring sign can also be seen in diseases characterized by abnormal reduced pulmonary arterial flow, such as proximal interruption of the pulmonary artery or chronic pulmonary thromboembolism. Occasionally, a small vascular opacity abutting a bronchus is a bronchial, rather than a pulmonary, artery.[79-82] See "Bronchiectasis".

AIR CRESCENT SIGN (*SINAL DO CRESCENTE AÉREO*)

The air crescent sign is a CT finding defined as a variable-sized, crescent- or half-moon-shaped collection of air in the periphery of a soft-tissue density nodule or mass (Figure S32). It is commonly described as an X-ray or CT finding of a fungus ball (aspergilloma), in which there is an air collection interposed between the wall of the preexisting cavity and the dependent intracavitary lesion. The air crescent sign has also been described in other diseases, such as angioinvasive pulmonary aspergillosis, lung abscess, lung cancer, and other fungal infections.[72-74]

HALO SIGN (*SINAL DO HALO*)

The halo sign is a nonspecific CT finding defined as a halo of ground-glass opacity surrounding a nodule or, less commonly, a mass or a rounded area of consolidation (Figure S33). In most cases, the halo of ground-glass opacity represents perinodular hemorrhage.[4] In cases of angioinvasive aspergillosis (AIA), for example, the nodule represents pulmonary infarction secondary to fungal angioinvasion and the surrounding halo of ground-glass opacity represents perinodular alveolar hemorrhage. In other infectious processes, the halo sign represents perilesional inflammatory infiltration. In cases of adenocarcinoma, the halo sign represents tumor cell proliferation along the alveolar septa, with preservation of the lung architecture (lepidic growth).[1] The same features can be seen in some cases of metastatic adenocarcinoma (particularly in cases of adenocarcinoma originating from the gastrointestinal tract or pancreas). As an initial diagnostic approach, it is useful to determine patient immune status. In immunocompromised patients, the halo sign is most commonly due to infectious diseases, the most common being invasive fungal diseases, such as AIA. Therefore, in the presence of febrile neutropenia, especially in patients with hematologic malignancies and in bone marrow transplant recipients, AIA is the major cause of the halo sign.[1] In such cases, the halo sign is considered to constitute early evidence of AIA, warranting initiation of antifungal therapy before serologic test results are known.

REVERSED HALO SIGN (*SINAL DO HALO INVERTIDO*)

The reversed halo sign (RHS) is defined as a rounded area of ground-glass opacity surrounded by a ring of consolidation.[1] The RHS was first described as a sign specific for OP. Later studies identified RHS in a wide spectrum of infectious and noninfectious diseases.[4,83-86] The most common infectious causes of RHS are tuberculosis, paracoccidioidomycosis, and invasive fungal diseases (invasive pulmonary aspergillosis and mucormycosis).[87] Among noninfectious diseases, both idiopathic or secondary OP is the most common cause. Other important causes are pulmonary infarction and sarcoidosis (Figure S34).[1] Although RHS is considered a nonspecific sign, a careful analysis of its morphological characteristics can narrow the differential diagnosis, helping the attending physician to make a definitive diagnosis. Two imaging patterns should be taken into account in order to make the diagnosis more specific: the presence of nodules on the wall of and/or within the halo (nodular RHS); and a reticular pattern within the halo (reticular RHS). It should be borne in mind that these two patterns are not found in OP, which is the most common cause of RHS. These considerations are important because the treatment for these conditions is completely different.

BEADED SEPTUM SIGN—STRING-OF-BEADS SIGN/ROSARY SIGN/NODULAR SEPTAL THICKENING (*SINAL DO SEPTO NODULAR — SINAL EM CONTAS/SINAL EM ROSÁRIO/ESPESSAMENTO SEPTAL NODULAR*)

Interlobular septa surround the secondary pulmonary lobule and are composed of connective tissue, pulmonary veins, and lymphatics. Normal interlobular septa are usually not visible on radiological imaging but can sometimes be seen on HRCT, in which case they appear few in number, thin, and in the lung periphery.[33] Edema, inflammatory infiltrates, fibrosis, and neoplastic spread can lead to interlobular septal thickening, which can be smooth, irregular, or nodular. Nodular septal thickening is often associated with lymphangitic carcinomatosis or sarcoidosis, and, less often, it can also be seen in other lymphoproliferative disorders, in pneumoconiosis, and in amyloidosis.[1] On X-rays, it is difficult to determine whether the thickening is smooth or irregular/nodular, and the septal or reticular pattern of interstitial opacities is usually identified. Both CT and MRI allow us to identify nodular thickening of the interlobular septum, which takes on the appearance of a string of beads or rosary. In lymphangitic carcinomatosis, the beaded septum sign is most often focal and unilateral, being associated with unilateral hilar/mediastinal adenopathy and other suspicious changes in patients with a history of malignancy (Figure S35). In sarcoidosis, the beaded septum sign is most commonly bilateral and symmetric, seen predominantly in the middle and upper fields of the lungs, associated with bilateral hilar adenopathy, as well as in the right paratracheal stations. Sarcoidosis typically affects Black women between 20 and 40 years of age.[88]

THORACOLITH/THORACOLITHIASIS (*TORACOLITO/TORACOLITÍASE*)

A thoracolith is defined as a small, free, and mobile structure/nodule, with or without calcification, in the pleural cavity (Figure S36). Thoracolithiasis is a rare benign condition characterized by the presence of one or more thoracoliths in the pleural cavity. The most characteristic radiological finding is mobility of the small structure/nodule, which can be demonstrated by sequential imaging or by changing patient position.

Thoracolithiasis is rarely symptomatic, being diagnosed on the basis of an incidental finding on X-rays or CT, and require no specific treatment, nor surgical resection.[89]

FINAL CONSIDERATION

Although this article is not definitive, we believe that it can help radiologists to attempt standardization of reports, which should improve understanding of reports and result in better patient care.

AUTHOR CONTRIBUTIONS

BH, CNA, and ASSJ: conception and planning of the study; and interpretation of results. All authors: drafting or revision of the preliminary and final versions; and approval of the final version.

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Impact of exposure to smoke from biomass burning in the Amazon rain forest on human health

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ABSTRACT

This review study aimed to determine the relationship between exposure to smoke from biomass burning in the Amazon rain forest and its implications on human health in that region in Brazil. A nonsystematic review was carried out by searching PubMed, Google Scholar, SciELO, and EMBASE databases for articles published between 2005 and 2021, either in Portuguese or in English, using the search terms "biomass burning" OR "Amazon" OR "burned" AND "human health." The review showed that the negative health effects of exposure to smoke from biomass burning in the Amazon have been poorly studied in that region. There is an urgent need to identify effective public health interventions that can help improve the behavior of vulnerable populations exposed to smoke from biomass burning, reducing morbidity and mortality related to that exposure.

Keywords: Fires; Air pollution; Risk factors; Risk assessment; Rainforest; Brazil.

INTRODUCTION

The Amazon is the largest tropical rain forest in the world, covering an area of 5.5 million km^2, the majority of the area (60%) being located in Brazil. It represents half of the remaining tropical forest area and has the greatest biodiversity in the world. About 27 million people live in the area known as "Legal Amazon" area in Brazil (Figure 1), which includes nine Brazilian states.[1,2]

The Amazon rain forest has two distinct seasons. High precipitation volumes are observed in the rainy season (> 250 mm/month), which typically occurs between December and March. It also rains in the dry season, which occurs between May and September, but precipitation is lower (20-70 mm/month).[3] Forest fires predominate during the dry season,[4] with a tenfold increase in atmospheric pollutant concentrations,[5] impacting human health.[6]

This review study aimed to determine the relationship between exposure to smoke from biomass burning in the Amazon rain forest and its implications on human health in that region in Brazil

DATA SOURCE

A nonsystematic literature review was carried out by searching PubMed, Google Scholar, SciELO, and EMBASE databases for articles published between 2005 and 2021, in Portuguese or English, using the following search words: "biomass burning" OR "Amazon" OR "burned" AND "human health." The bibliographic search was conducted between November of 2020 and May of 2021. A total of 126 scientific articles were initially retrieved, of which 72 effectively contemplated the theme of fire smoke in the Brazilian Amazon and its repercussions on human health. In addition, the Brazilian National Institute for Amazon Research[7] database was consulted.

FIRES OR WILDFIRES?

Amazon fires can be classified into three major types.[8,9] The first type is deforestation fire, which includes clear-cutting of the forest that is left to dry and the subsequent burning of cut trees as a means of preparing the soil for agriculture and cattle farming.[8] The second type of fire is associated with the maintenance of previously cleared areas to eliminate cut trees and clear weeds for agricultural

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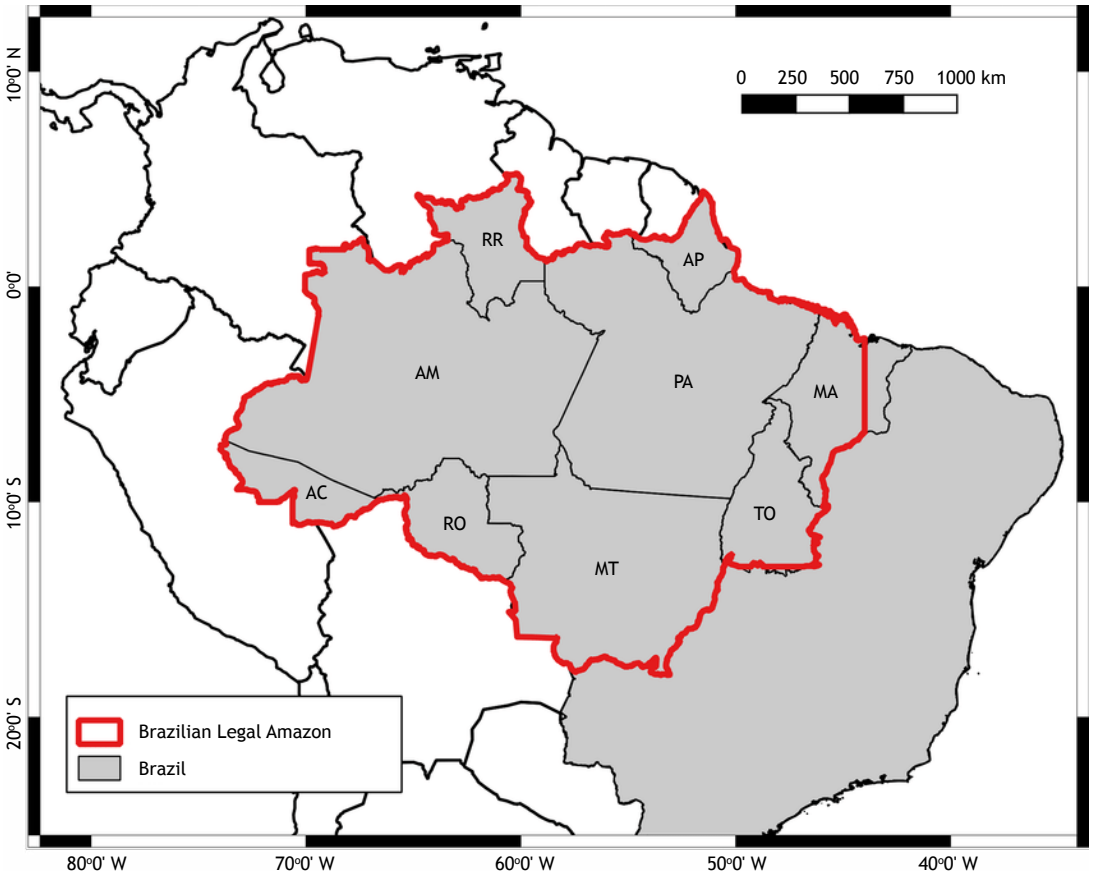

Figure 1. Brazilian Legal Amazon boundaries, including nine federal states. AC: Acre; AM: Amazonas; AP: Amapá; MA: Maranhão; MT: Mato Grosso; PA: Pará; RO: Rondônia; RR: Roraima; and TO: Tocantins. Modified from Müller-Hansen et al.[1]

and cattle farming activities. This type of fire can dry out the surrounding forest and increase vulnerability to fire in subsequent years. Not all fires in previously cleared areas are intentional, and some expand beyond the intended limits.[8] The third type of fire is called wildfires, which consume the standing forest, either for the first time, where the flames are mainly restricted to the understory, or as repeated events, resulting in more intense fire.[8]

Deforestation, maintenance of cleared areas, and forest fires account for 8%, 39%, and 53% of fire outbreaks,[9] respectively, with distinct social and environmental impacts.[8] However, all of these events result in significant pollutant emissions into the atmosphere. In the Amazon, the different types of fires are of anthropic origin, because natural fires rarely occur[9] due to the high moisture content in the soil and vegetation.[10-14]

Intense droughts occurred in 2005, 2007, and 2010, which increased the number of human-caused fires. Because of this, fires in the Amazon have become a persistent environmental problem, partially linked to the growing incidence of deforestation that should not be underestimated, but rather considered when implementing measures to protect the Amazon rain forest.[9,15] Nevertheless, a recent study reported a reduction in deforestation rates between 2004 and 2012, with a 30% decrease in particulate matter (PM) concentrations during the dry season, preventing up to 1,700 premature deaths per year and demonstrating the direct benefits of maintaining forest areas.[11,16]

To date, independent estimates indicate that 15-20% of natural forest cover in the Legal Amazon has been deforested.[2,10,17-19] The latest report from the 2019 Greenhouse Gas Emissions and Removal Estimating System[17] indicated that deforestation, especially in the Amazon, increases the emissions of pollutants. In the last five decades, the amount of greenhouse gases released into the atmosphere by the land-use change sector increased to 23% and accounts for 44% of the total emissions in Brazil.[18]

If the deforested area continues to increase, there is a possibility of reaching a tipping point where the ecosystem will have no resilience to recover, being gradually transformed into a degraded tropical savannah landscape.[15] Synergies between deforestation and climate change are estimated to make forests hotter and drier, and thus, more likely to sustain uncontrolled fires[8,19] with impacts on human health.[3,20] Regional climate projections suggest that fire regimes in the

Amazon will intensify, affecting the outdoor and indoor air quality in rural and urban communities.[13,15,20,21]

FIRE EMISSIONS AND AIR QUALITY

Forest fire emissions are physically and chemically complex; smoke formation, physical weathering, chemical weathering, and atmospheric transport are influenced by several factors such as fuel type, fire type, landscape characteristics, rate of fuel consumption, and weather conditions.[22,23]

The main primary emissions that aggravate air quality and remain a public health concern include PM, carbon monoxide, nitrogen oxide, benzene—which is a primary volatile organic organic compound—and trace metals. Air quality is further affected by the formation of secondary pollutants such as ozone, secondary VOCs (such as acetone), and polycyclic aromatic hydrocarbons (PAHs). However, these secondary products are even more difficult to predict due to the various factors involved.[24-27]

The northern region of Brazil has no continuous air quality monitoring networks,[28] except for a pioneering initiative established by the Federal University of Acre, which started monitoring PM with a mean diameter of < 2.5 μm ($PM_{2.5}$) in 22 cities in the state of Acre in 2019.[29] Results showed that, during the dry season, the mean $PM_{2.5}$ concentration in the 22 cities was around 40 μg/m³, often exceeding the limit recommended by the WHO (24-h mean of 25 μg/m³).[5,29,30]

The chemical $PM_{2.5}$ composition from Amazonian wildfires shows a predominance of organic compounds (about 80%), containing 10-15% of smoke particles known as black carbon. Inorganic compounds correspond to 10-20% of $PM_{2.5}$, sulfates being the most abundant ones.[30]

The levels of PAHs and VOCs present in smoke from Amazonian fires can be relatively high and include potentially carcinogenic substances, such as pyrene (benzo[a]pyrene equivalent), formaldehyde, and benzene.[31] Recurrent exposure to smoke emissions may increase the risk of cancer in the exposed population.[23] A study conducted in the state of Rondônia showed that the risk of lung cancer due to long-term exposure to benzo[a]pyrene equivalents present in fire smoke emissions was twice as high as that recommended by the WHO.[32]

Some particles can remain in the atmosphere for days to weeks and travel long distances, sometimes hundreds of kilometers,[23,24] affecting the concentration of pollutants in regions far from the source. As examples, we can mention the presence of particles from the Australian forest fires in the city of Porto Alegre in early 2020[33] and that from the Amazon basin and Bolivia in the city of São Paulo in August of 2019,[34] as well as that on the Andean snow layer and glaciers shown in satellite images, raising the hypothesis that part of the black carbon found in that region was possibly originated from fires in the Amazon.[35]

AIR POLLUTION AND HEALTH EFFECTS

Three main mechanisms explain the biochemical, physiological, and clinical effects of exposure to air pollution particles.[27] First, inhaled particles can react with pulmonary neural receptors and activate the reflex that is involved in the chemical and electrical communication between the lung and the nervous system. The return signals from the brain that travel through the autonomous nervous system can trigger an increase in blood pressure levels and changes in heart rhythm.[25] Second, air pollutants interact with alveolar-capillary membranes and generate oxidative stress reactions, as well as local and systemic inflammatory responses.[36] These responses induce oxidation and blood lipid disorders, platelet activation, and prothrombotic changes in proteins, affecting blood vessel functions and increasing blood coagulation.[25] Third, ultrafine $PM_{0.1}$ (mean diameter < 0.1 μm) can be translocated across the alveolar membrane and act systemically at a distance from the lung.[31]

Biochemical and physiological responses contribute to a series of functional changes, including endothelial dysfunction, as well as lesion activation and formation. Local changes in the lungs increase pulmonary responses that can affect airway function and decrease resistance to viruses and bacteria, increasing the risk of infections.[24,37]

FOREST FIRE SMOKE AND HEALTH EFFECTS

Emission and atmospheric transport of smoke from forest fires are a growing and costly global public health problem that mainly affects vulnerable communities and more sensitive people, such as children (infants and toddlers), pregnant women, fetuses, middle-aged people, the elderly (> 65 years of age), people with lung and/or heart disease, (active and passive) smokers, workers prone to occupational diseases, and socially vulnerable populations.[38-42]

The physical and chemical characteristics of air pollutants, whether from urban areas or wildfire emissions, are dynamic, varying in time and space; hence, the assessment of their impacts remains a challenge. In addition, current efforts to study the effects of smoke from forest fires are limited due to the lack of air quality measurements in the northern region of Brazil.[28] Table 1 lists some of the most relevant studies on the effects of wildfire smoke in the Amazon on human health in Brazil.

Forest fire smoke consists mainly of PM, especially $PM_{0.1}$. The PM concentration is higher close to the emitting source. During periods of active fire, $PM_{2.5}$ was significantly associated with respiratory effects due to the direct deposition of inhaled particles in the lungs, consequently causing local oxidative stress and inflammation and being potentially likely to overflow into systemic circulation.[25,36]

Previous studies showed that lung cell exposure to PM_{10} (mean diameter < 10 μm) significantly increases

Table 1. Main studies evaluating the effects of fire smoke on human health in the Brazilian Amazon.

Study	Year	City or region	Pollutants considered	Population group	Outcome studied	Type of study
Mascarenhas et al.[47]	2008	Rio Branco, AC	$PM_{2.5}$	Several age groups	Respiratory disease-related ER visits	Ecological time-series study
Carmo et al.[37]	2010	Alta Floresta, MT	$PM_{2.5}$	Several age groups	Outpatient visits due to respiratory disease	Epidemiological study
Ignotti et al.[48]	2010	Tangará da Serra and Alta Floresta, MT	$PM_{2.5}$	Children and older people	Hospitalizations due to respiratory disease	Ecological time-series study
Prass et al.[50]	2012	Porto Velho, RO	Number of fires	Children and pregnant women	Low birth weight	Retrospective cohort study
Carmo et al.[42]	2013	Rio Branco, AC	$PM_{2.5}$	Children	Hospitalizations due to respiratory diseases	Ecological time-series study
Andrade Filho et al.[46]	2013	Manaus, AM	$PM_{2.5}$	Children	Hospitalizations due to respiratory disease	Ecological time-series study
Jacobson et al.[44]	2014	Tangará da Serra, MT	PM_{10}, $PM_{2.5}$, "black carbon"	Children	Changes in PEF	Longitudinal study
Cândido da Silva et al.[49]	2014	Tangará da Serra and Alta Floresta, MT	$PM_{2.5}$ and CO	Children and pregnant women	Low birth weight	Retrospective cohort study
Reddington et al.[16]	2015	Amazon	$PM_{2.5}$	Several age groups	Premature deaths	Computational modeling and risk assessment
de Oliveira Alves et al.[31]	2015	Porto Velho, RO	PM_{10} and PAH	N/A	N/A	Chemical characterization of PM_{10} and health risk assessment
Silva et al.[45]	2016	Rio Branco, AC	O_3 and $PM_{2.5}$	Children	N/A	Toxicological risk assessment
de Oliveira Alves et al.[32]	2017	Porto Velho, RO	PM_{10} and PAH	N/A	Toxic and mutagenic effects on lung cells	Exposure tests of lung cells to fire PM_{10}
de Oliveira et al.[36]	2018	Porto Velho, RO	$PM_{2.5}$ and Hg	Children and teenagers	Oxidative stress biomarkers	Cross-sectional study
Nawaz et al.[51]	2020	Amazon	$PM_{2.5}$	Several age groups	Premature deaths	Computational modeling and risk assessment

$PM_{2.5}$: particulate matter with a diameter < 2.5 μm; PM_{10}: particulate matter with a diameter < 10 μm; CO: carbon monoxide; PAH: polycyclic aromatic hydrocarbons; AC: Acre; RO: Rondônia; AM: Amazonas; and MT: Mato Grosso.

the levels of reactive oxygen species and inflammatory cytokines, the risk of autophagy, and DNA damage. Continued exposure to PM_{10} activates cell apoptosis and necrosis.[32] Respiratory morbidities include asthma, COPD, bronchitis, and pneumonia.[43-46] Poor socioeconomic conditions increase the association between exposure to $PM_{2.5}$ from forest fires and hospital and ER admissions due to asthma and heart failure.[6,41,47,48]

A significant and positive relationship was found between ozone concentrations during the fire period and ER admissions due to asthma[6] in areas surrounding a forest fire. Heavy smoke can cause eye irritation, corneal abrasions, and a significant reduction of visibility, increasing the risk of traffic accidents.[40]

The fetus can also be exposed to high PAH levels in the uterus, which is particularly worrisome in early life because this exposure can occur during the so-called

"susceptibility window", a period that impacts structural mechanisms and cell signaling and that can result in the development of diseases in adulthood.[25] The exposure of pregnant women to PM in the first trimester of pregnancy has been associated with a higher risk of low birth weight. That exposure at any time during pregnancy increases the risk of preterm birth.[25,49,50]

Children are especially vulnerable to PM exposure. Because they are in growing and developing, they have greater tidal volume in proportion to their body weight, less efficient nasal filtering, which facilitates that particles move deeper into their lungs, and greater outdoor exposure. In addition, as they have long life expectancy, the adverse effects of that exposure may have lifelong consequences. Even healthy children may experience upper airway symptoms, as well as increased coughing and wheezing, when exposed to forest fire smoke.[25]

People living in areas affected by forest fires have presented an increased risk of mental illness, including post-traumatic stress disorder, depression, and insomnia, due to traumatic experiences, loss of property, and need for displacement.[40]

Biomass burning fire emissions across Brazil significantly contribute to premature deaths, the largest fires occurring in the northern region of Brazil. Nawaz et al.[51] reported that premature deaths were attributed to fire emissions and accounted for 10% of all $PM_{2.5}$-related premature deaths in Brazil during the 2019 fire season.

FIRES AND COVID-19

Recent studies have established pathophysiological factors and epidemiological associations between PM exposure and viral infections.[52] Landguth et al.[53] recently reported that exposure to high $PM_{2.5}$ concentrations during the forest fire season might positively be associated with increased incidence of influenza in the following season.

The association between air pollution and incidence of COVID-19 has been documented.[54] PM can carry viruses indoors, impair immunity, increase individual susceptibility to pathogens, and facilitate the entry of viruses into the respiratory tract, possibly causing more serious infections.[55]

Recent ecological studies suggest a link between exposure to high $PM_{2.5}$ levels and increased COVID-19[56] mortality, although the influences of other factors, such as population density, socioeconomic factors, and compliance with social distancing measures, should also be considered.[21,57]

Populations more vulnerable to forest fire smoke exposure are also susceptible to SARS-CoV-2 infection. Exposure to wildfire smoke may also increase the likelihood of SARS-CoV-2 infection, as well as the severity of COVID-19.[58]

A study in the city of San Francisco, one of the regions affected by forest fires in California, USA, documented a positive association of $PM_{2.5}$ and carbon monoxide levels with increased numbers of daily cases of SARS-CoV-2 infection, highlighting the important contribution of such environmental pollutants as triggering factors for COVID-19 and mortality. The increased incidence of COVID-19 and associated deaths were also related to exposure to environmental forest fire pollutants ($PM_{2.5}$, carbon monoxide, and ozone) in ten different localities in the state of California.[58,59]

According to Navarro et al.,[60] the concomitant occurrence of SARS-CoV-2 infection and inhalation of forest fire smoke may increase the risk of COVID-19 among forest firefighters due to the transport of SARS-CoV-2 by PM and regulation of angiotensin-converting enzyme II, facilitating the entry of the virus into epithelial cells. Exposure to smoke from uncontrolled fires may also increase the risk of developing more severe forms of COVID-19, such as cytokine release syndrome, hypotension, and ARDS.[60]

Increased deforestation and the specter of drought may worsen the COVID-19 pandemic and endanger the lives of people living in the Amazon.[61] Fires from the Amazon account for 80% of the regional $PM_{2.5}$ pollution increase and affect 24 million Amazonians. Thus, we highlight that the potential relationship between $PM_{2.5}$ exposure and COVID-19 has special relevance to public health in Brazil, where infection and mortality rates are among the highest in the world,[62] especially in vulnerable populations who may be highly exposed (e.g., indigenous people, whose COVID-19 mortality rates are almost twice as high as the Brazilian average).[21]

Manaus, the capital of the state of Amazonas, was one of the Brazilian cities most affected by the COVID-19 pandemic. A previous study on serum antibody detection indicated that 76% of the population of Manaus had been infected by SARS-CoV-2 until October of 2020, a percentage higher than that estimated to reach collective immunity (67%).[63] In Manaus, the so-called first wave peaked in April of 2020, reaching 120 deaths per day due to ARDS. In this context, the strong resurgence of COVID-19 in January of 2021 was surprising, immune evasion and increased transmissibility of SARS-CoV-2 variants being indicated as possible causes.[64] It is interesting to note that the peaks of the first and second waves of COVID-19 in Manaus occurred during the rainy season, when fires are not common. This fact suggests the absence of a direct association between short-term exposure to wildfire emissions and COVID-19 morbidity and mortality in the region. However, long-term exposure may increase the vulnerability of the population to viral infections. A recent study reported that the spatial distribution of COVID-19 in Brazil stems from multiple causes, including health care service inequalities, the flow of people and connection networks between cities, as well as the lack of national coordination and synchrony in the implementation of nonpharmacological measures to contain the spread of the virus, such as the use of masks and mobility restrictions.[65]

AIR QUALITY MONITORING NETWORKS

Increased awareness of the health risks posed by wildfires compels public health authorities and health care professionals to advise at-risk people to adopt measures that will prevent exposure to wildfire smoke.[25,66]

One primary source of available and up-to-date information to assist public health and health care professionals is the Wildfire Smoke: Guide for Public Health Officials[67]: it is a useful guideline to help public health officials prepare for wildfire smoke and provides information that can be shared with the public in order to protect themselves during such events.

Emission containment (land/fire management practices) and preventive efforts against exposure, in addition to the identification of susceptible populations, can help prepare for air pollution episodes and ensure that the population at risk will be evacuated from harmful areas when the events threaten their safety. Hence, effective public health communication strategies should be developed in collaboration with communities, public health officials, health care professionals, state officials, and fire officials, because the impacts of wildfire smoke on public health will continue to increase.[68-71]

It is essential to expand the air quality monitoring network in the states included in the Legal Amazon. Without such monitoring, the size of the environmental problem related to exposure to pollutants emitted by fires cannot be determined. This hinders the creation of effective public policies to reduce this problem. State environmental agencies are responsible for monitoring air quality, disseminating accurate and clear information about it, and providing optimal communication through public awareness campaigns aimed at empowering people to modify their behavior in order to improve their health and the quality of the air they breathe.[24]

GENERAL RECOMMENDATIONS FOR REDUCING EXPOSURE IN AREAS WITH FOREST WILDFIRE/FIRE SMOKE[67]

- Avoid strenuous or prolonged work: if a person is working outdoors, pay attention to the occurrence of symptoms; they are an indication that exposure needs to be reduced
- Reinforce hydration for airway protection
- If it is necessary to advise the patient to stay indoors, indoor air should be kept as clean as possible
- If air conditioning systems are used at home, keep the fresh air inflow closed and the filter clean to prevent additional particles from contaminating indoor air
- If there are no air conditioning systems at home, staying indoors with the windows closed in extremely hot weather can be dangerous; the use of alternative shelters, such as staying at a relative's or a friend's place or at a shelter with cleaner air, is recommended
- If driving is necessary, turn on the car's air conditioning system in recirculation mode to prevent smoky air from entering the car, although the capacity of these filters is limited
- Avoid activities that increase indoor pollution, such as the use of anything that burns (wood-burning fireplaces, gas stoves, candles, incense sticks, mosquito repellent devices, among others)
- Patients should be encouraged to quit smoking, because smoking increases the amount of pollutants in the lungs of smokers and those around them
- Advise your patients to visit a referral health care facility when presenting with new cardiovascular or respiratory symptoms or if other existing health problems worsen

FINAL CONSIDERATIONS

Exposure to wildfire emissions is an important and growing clinical and public health problem. Weather pattern changes, including droughts, increase the risks for wildfires and comorbidities. Exposure to Amazon wildfire smoke impacts the health of populations at a higher risk, including those with heart or chronic lung disease, the elderly, children, pregnant women, and fetuses.

Public policies are needed to improve the communication of actionable information by public health care professionals so that populations prone to being exposed to fire smokes are able to act accordingly, improving their health and quality of life effectively.

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Use of extracorporeal membrane oxygenation in the management of severe tracheobronchial injuries

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TO THE EDITOR,

Tracheobronchial injuries are rare entities that are associated with high morbidity and mortality. Therefore, their early and prompt diagnosis is essential to readily allow for the correct choice of therapeutic approach.[1,2] Complex cases may require the use of extracorporeal membrane oxygenation (ECMO), enabling the use of low airway pressures, thus allowing for a safe surgical procedure.[3,4] In this sense, herein, we describe three cases of patients with airway lesions, in which venovenous ECMO (V-V ECMO) was used as support for surgical treatment.

Initially, we present a 19-year-old female patient, a victim of a car accident, admitted to a trauma hospital in need of orotracheal intubation and pleural drainage due to bilateral pneumothorax. After 15 days of hospitalization, air leaks persisted through both surgical drains; thus, she underwent fiberoptic bronchoscopy, which revealed a laceration of the trachea that started in the cervical region and extended to the right main bronchus, with concomitant esophageal rupture. Due to the severity of the tracheoesophageal lesion and the difficulty in maintaining a safe airway, the patient was transferred to a tertiary hospital 15 days after the initial care. Shortly after arriving at the hospital, the staff unsuccessfully attempted to position the orotracheal tube in the left main bronchus and, due to the difficulty in maintaining satisfactory ventilation and the presence of respiratory acidosis and hypoxemia *(*pH 7.1; pO_2 65.2 mmHg; pCO_2 109 mmHg, PaO2/FiO2 ratio 76 mmHg*)*, it was decided that V-V ECMO should be indicated. The right common femoral vein was cannulated for venous blood drainage, as was the right internal jugular vein for return of oxygenated blood, with 23 Fr and 19 Fr cannulas, respectively. Support was initiated with a blood flow of 4 L/min and a gas flow of 5 L/min. Upon immediate stabilization of the patient's oxygenation, surgical correction was planned for the following day through a right thoracotomy and cervicotomy to close the tracheal laceration with the interposition of an intercostal muscle flap due to complete necrosis of the membranous tissue, in addition to an esophagectomy. ECMO was continued for 20 days, ensuring flap healing by low ventilatory pressures. The patient evolved favorably and was discharged on the 58th day of hospitalization.

The second case was of a 36-year-old female patient with Steinert's myotonic dystrophy who underwent surgical resection of a large mass in the right hemithorax, diagnosed as pulmonary sarcoma, and neoadjuvant radiotherapy. In the transoperative period, all lobes were found to be affected, and for this reason, a pneumonectomy was performed. Following extubation on the first postoperative day, the patient required new orotracheal intubation 2 days later due to acute respiratory failure and septic shock. She underwent tracheostomy and remained on ventilatory support for 14 days. On the 28th postoperative day, she again presented hemodynamic instability and respiratory failure, thus requiring mechanical ventilation. Chest X-ray showed a reduction in the air-fluid level in the right lung and consolidations in the left lung. Bronchoscopy revealed a 5 mm fistula in the right bronchial stump. Drainage of the right pleural cavity and subsequent installation of the V-V ECMO was carried out due to hypoxemia and hypercarbia (pH 7.09; pCO_2 101 mmHg; PaO_2/FiO_2 122 mmHg), in addition to significant air leakage through the fistula. The right and left femoral veins were cannulated since the jugular veins presented thrombosis. ECMO was required for a total period of 12 days, and, 4 days later, a classical pleurostomy was performed. The patient was discharged after 79 days of hospitalization.

The last case involved a 36-year-old male patient with odynophagia and dental infection who, after seeking medical care, received symptomatic medications and antibiotic therapy. After seven days, he exhibited clinical worsening associated with fever, which led him to undergo a new medical evaluation. Cervical and thoracic computed tomography were compatible with descending necrotizing mediastinitis: collection with gaseous content in the cervical region, extending to the pre-esophageal region. The patient was referred to a tertiary hospital, where he was submitted to a cervicotomy for drainage of the cervical abscess, and a right posterolateral thoracotomy, with drainage of the pleura and mediastinum. In the first days after the procedure, he evolved favorably; however, on the 4th postoperative day, the patient presented air leakage through the chest drains, as well as contralateral pneumothorax. Fiberoptic bronchoscopy revealed a fistula in the right main bronchus, in addition to a large amount of purulent secretion. The orotracheal tube was placed in the left main bronchus, and conservative treatment was performed initially. However, a worsening of ventilatory parameters was observed, with arterial blood gases presenting a PaO2/FiO2 ratio of 126 mmHg, associated with bilateral pneumonia. Thus, a V-V ECMO with cannulation of the right and left femoral veins was installed due to cervical infection. Immediately after

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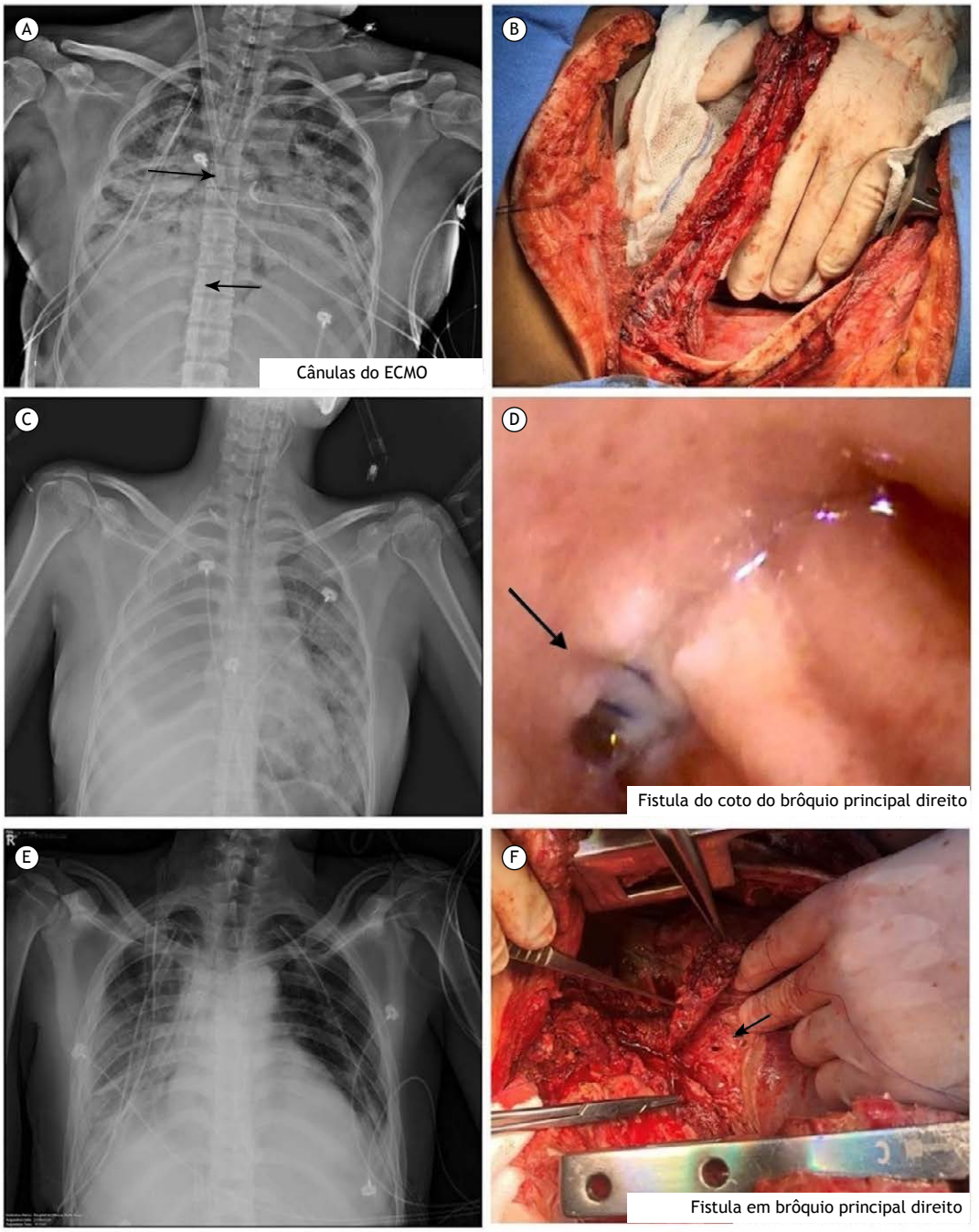

Figure 1. Images of the described case reports. Case 1: (A) chest X-ray with arrows indicating the position of the ECMO cannulas; (B) intercostal muscle flap. Case 2: (C) chest X-ray evidencing the pneumonectomy cavity to the right and pulmonary consolidations to the left; (D) right main bronchus stump with arrows indicating the location of the fistula. Case 3: (E) chest X-ray after cannulation of the right and left femoral veins; (F) arrow indicating the location of the fistula during the transoperative period.

placement of the ECMO, a new surgical approach was conducted, with debridement of the edges of the fistulas and placement of an intercostal muscle flap over the defects of the right main bronchus. ECMO was continued for another 12 days, which allowed for early extubation on the 2nd postoperative day and the maintenance of low ventilatory pressures in the airway, ensuring the healing of the repaired fistula.

Even today, the vast majority of surgeries involving the airways do not require extracorporeal support to be performed. Nevertheless, in complex injuries, the use of ECMO may be necessary in order for surgical repair to be carried out.[5] This method has proven to be a useful tool in the therapeutic arsenal of the thoracic surgeon, and case reports around the world confirm its feasibility and safety.[6,7,8] Unfortunately, in Brazil, this

technique is still costly, being, therefore, little used in such situations.[9] A brief literature review revealed that only one healthcare service in our country reported two cases where ECMO was used for complex oncological resections involving the airways.[10] Thus, we believe that our thoracic surgery service is the first to report three cases of patients who used ECMO for the surgical correction of airway injuries. In our experience, this method seems to be a satisfactory and safe option for ventilatory support in patients undergoing complex surgeries, enabling the use of low airway pressures and ensuring adequate postoperative healing.

AUTHOR CONTRIBUTIONS

BMP: writing and reviewing the manuscript. DCM: supervising the editing of the manuscript. WL: reviewing the manuscript. AMQ: writing and reviewing the manuscript. MGS: reviewing and approval of the final manuscript.

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Acute exacerbation of post-COVID-19 pulmonary fibrosis: air travel as a potential trigger

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TO THE EDITOR,

Pneumonia secondary to coronavirus disease 19 (COVID-19) has been the leading cause of hospitalization and death in affected patients during the ongoing pandemic, mainly due to acute hypoxemic respiratory failure. However, to date, long-term follow-up data from the increasing number of recovered patients, especially those with severe disease and mechanical ventilation requirements, remain scarce.[1] Persistent physiological impairment[2] and even late response to corticosteroid treatment for post-COVID-19 interstitial lung disease (ILD) have been described, particularly in the context suggestive of the presence of organizing pneumonia (OP).[1,3]

Acute exacerbation (AE) of ILD was initially reported for idiopathic pulmonary fibrosis (IPF) and is currently best defined as an acute worsening or development of dyspnea, associated with new bilateral ground-glass opacities (GGO) and/or consolidations superimposed in a pattern consistent with usual interstitial pneumonia (UIP), not fully explained by cardiac failure or fluid overload, in patients with a previous or concurrent diagnosis of IPF.[4] AE has been described in ILDs other than IPF and is often associated with a poor prognosis.[5]

Herein, we describe the case of a 68-year-old male admitted to our hospital due to COVID-19 (confirmed by RT-PCR from nasal swab), who presented dyspnea and became hypoxemic twelve days after the onset of symptoms. His comorbidities included mild hypertension, dyslipidemia, and coronary artery disease. He had no history of respiratory disease, and a CT scan of the chest performed a few days after symptom onset revealed only sparse GGO, with no sign of chronic lung disease (Figures 1A and 1D).

The patient required progressively increasing respiratory support, initially through a nasal cannula, then high-flow oxygen cannula (HFNC) and non-invasive ventilation, and, finally, invasive mechanical ventilation (MV). The lung-protective ventilation strategy was assured throughout treatment, a cycle of prone positioning was needed, and estimated respiratory system static compliance was 20 mL/cmH_2O. After eight days, the patient was completely weaned from MV and successfully extubated but still required oxygen treatment with HFNC for 11 days due to persistent hypoxemia. Motor rehabilitation was initiated for critical illness polyneuropathy and resting hypoxemia, with the need for low-flow nasal cannula support; a persistence of accentuated exercise-induced desaturation was observed. Oxygen requirements slowly and progressively decreased, and around one month after extubation, he remained on room air at rest, with mild desaturation during exercise.

A CT scan of the chest, performed two months after symptom onset, showed persistent GGO with predominantly peripheral distribution in the upper lobes, in addition to reticulation, GGO, traction bronchiectasis, and areas of architectural distortion in the lower lobes, suggesting the presence of post-COVID-19 pulmonary fibrosis (Figures 1B and 1E). Corticosteroid treatment was used throughout hospitalization, with a slow taper regimen, due to persistent physiological impairment and a presumed benefit from extended regimens.[6] At discharge, approximately 75 days after hospitalization, the patient seemed better, tolerating exercises in the rehabilitation center with small oxygen requirements and a peripheral oxyhemoglobin saturation of 93% on room air. The patient traveled by plane back to his hometown, with instructions for supplemental oxygen usage during the flight.

The flight lasted two hours and was otherwise uneventful, except for increasing oxygen requirements. Upon arrival, increasing dyspnea and oxygen requirements at rest were noted. Twelve hours after arrival, the patient was readmitted to the hospital due to worsening dyspnea and hypoxemia. Laboratory tests demonstrated only a mild elevation of serum C-Reactive Protein and leukocytes. Pulmonary embolism and cardiac fluid overload were ruled out. A CT scan of the chest showed new diffuse GGO and consolidations (Figures 1C and 1F). A molecular panel of respiratory viruses was negative, except for persistent SARS-CoV-2 RNA detection. Blood and sputum cultures were negative. Empirical broad-spectrum antibiotics and high-dose corticosteroid treatment (approximately 2 mg/kg) were initiated, and the patient was again placed on HFNC oxygen support. Symptoms and hypoxemia resolved around three weeks later, and the patient was discharged with a recommendation of avoiding immediate air travel.

Post-COVID-19 ILD remains poorly understood, and the time of follow-up to determine the presence of irreversible changes without lung sampling has not yet been established. Nonetheless, many patients will present persistent CT abnormalities at 6-months of follow-up, and gas exchange impairment seems to be the most common

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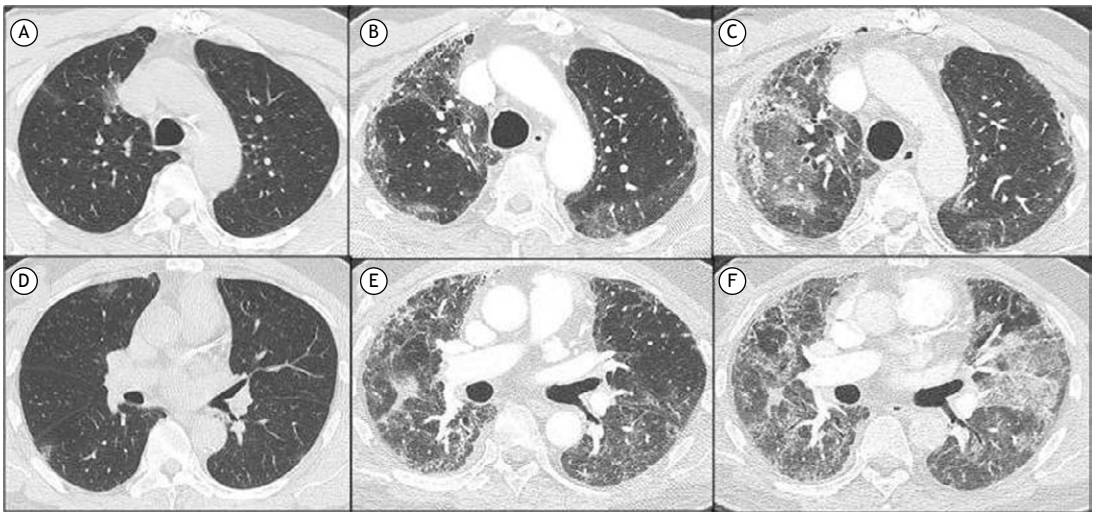

Figure 1. Chest CT scans demonstrating mild ground-glass opacities (GGO) and otherwise preserved lung parenchyma a few days after symptom onset (A and D); persistent peripheral GGO in the upper lobes and GGO, reticulation, and traction bronchiectasis in the lower lobes two months after symptom onset (B and E); new GGO and consolidations superimposed to the previous pattern on readmission (C and F).

physiological outcome; both may be related to initial disease severity.[1] Age, gender, the need for high-flow oxygen support and mechanical ventilation, and the extent and severity of lung involvement increase our patient's risk of developing pulmonary fibrosis as a long-term sequela of COVID-19.

AE-IPF and ARDS share many common pathophysiological features, including the overexpression of proinflammatory cytokines and histological patterns of diffuse alveolar damage, with clearly overlapping clinical-radiological criteria.[7] The AE of ILD was extensively reported and is currently classified as triggered by specific events, including infection, drug toxicity, and aspiration, or idiopathic, when no identifiable cause is present.[4,5] However, therapeutic interventions for AE have not been completely defined.

To our knowledge, AE in patients with post-COVID-19 ILD had not been previously reported, according to a review performed on May 13, 2021, searching the MEDLINE and Web of Science databases. Although the possibility of reinfection by COVID-19 cannot be completely ruled out as the etiology, we consider such a hypothesis unlikely based on the very short time from symptom onset to respiratory deterioration.

Migratory pulmonary infiltrates characterizing OP have been described in COVID-19 patients,[8] including delayed presentations,[9] particularly associated with hematologic malignancies.[8,9] However, lung infiltrates were acutely superimposed to persistent changes (seen throughout disease progression), rather than migratory, in our patient.

Additionally, air travel has been anecdotally reported as a potential trigger for AE-IPF, with presumed mechanisms of hypobaric-hypoxia inflammation and the recurrent mechanical stretching of the lungs.[10] Our patient received supplemental oxygen during the whole flight, although oxygen requirements increased during travel. Air travel for patients with lung diseases is generally deemed safe, although mild to moderate symptoms, including worsening dyspnea, seem to be very common,[11] and these patients are usually not followed up once they reach their destiny.

The number of patients with post-COVID-19 fibrosis will probably increase in the upcoming years, as COVID-19 has affected a large population around the world and is still ongoing. Further studies are warranted to answer two major questions raised by this report: 1- may post-COVID-19 fibrosis be marked by acute respiratory worsening, characterizing AE, similar to other fibrosing ILDs? 2- could air travel be a potential trigger of AE in ILDs?

AUTHOR CONTRIBUTIONS

AFA: study design, data collection, and writing and reviewing the manuscript. JMS: writing and reviewing the manuscript. RKF: writing and reviewing the manuscript. OGRN: data collection and writing and reviewing the manuscript. CRRC: writing and reviewing the manuscript. BGB: study design, data collection, and writing and reviewing the manuscript.

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Tobacco control in young people and adults: did Brazil do their homework?

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TO THE EDITOR:

Over the past 30 years, more than 200 million deaths have been caused by tobacco use and the annual economic costs arising from this use exceed US$1 trillion.[1-4] Updated data on smoking prevalence and the burden of disease attributable to Global Burden of Disease (GBD) 2019 are an urgent call to action for countries to program and implement stronger tobacco control policies than currently in place.[1,3,4]

These results demonstrate that in 2019, more than 1 billion people smoked tobacco regularly and nearly 8 million deaths were attributed to smoking, which accounted for 20.2% of all-cause deaths among men and was the main risk factor for deaths and DALY (Disability-adjusted life year) among men.[3,4] Among women, smoking was responsible for approximately 5.8% of all deaths, due to the lower prevalence, shorter duration and lower intensity of smoking among them compared to men.[3]

In 2019, the ten countries with the highest number of smokers combined comprised nearly two-thirds of the global smoker population and they are: China, India, Indonesia, the United States of America, Russia, Bangladesh, Japan, Turkey, Vietnam and the Philippines.[3]

The report points to important changes in prevalence globally when 1.14 billion (95% confidence interval [CI]:1.13-1.16) individuals were current smokers and consumed 7.41 trillion (95%CI:7.11-7.74) tobacco equivalents.[3] Between 1990 and 2019, there was a significant reduction in the prevalence of active smoking among men over 15 years of age in 135 countries (66%) and among women in only 68 countries (33%). In Brazil, the greatest reductions occurred, being 72.5% (95%CI:70.1-74.7) among men and 74.7% (95%CI:71.2-78.0) among women.[3]

The evolution of current smoking prevalence rates by age, considering the total group, showed the greatest reductions in Brazil (73.4% [95%CI:71.4-75.2]), Norway (53.5% [95%CI:49.1-57.6]), Senegal (50.9% [95%CI:44.6-56.0]), Iceland (49.7% [95%CI:44,5-54.1]), Denmark (49.3% [95%CI:46.4-52.2]), Haiti (47.5% [95%CI:40.5-54.4]), Australia (47.5% [95%CI:43.1–51.8]), Costa Rica (47.4% [95%CI:40.5–53.6]), Canada (47.4% [95%CI:42.4–52.0]) and Colombia (47.1% [95%CI:40.4–53.4]3.

The prevalence of smoking in 2019 among young people aged 15 to 24 remains high in many parts of the world with 20.1% (95%CI:19.4–20.8) among men and 4.95% (95% CI:4.64–5.29) among women. It is estimated that 82.6% (95%CI:82.1–83.1) of current smokers started the habit between 14 and 25 years of age, and that 18.5% (95%CI:17.7-19.3) started regularly at 15 years of age.[4] Starting tobacco use before age 20 highlights the unique window of opportunity to target prevention efforts among young people, save millions of lives and avoid future healthcare costs.[5]

The development and application of strong tobacco control policies have led to progress in protecting young people and reducing the number of young smokers in some countries. Brazil had the greatest reduction in the prevalence of smoking among individuals aged between 15 and 24 years, with a decrease in the prevalence of 74.5% (95%CI:69.0–78.9) ranging from 27.5% (95%CI:25.2-30.0) in 1990 to 7.01% (95%CI:5.9-8.3) in 2019.[6]

However, the prevalence of active smoking among young people, in most countries, remains high and is associated with the increased use of electronic cigarettes and vaporization products, which puts the progress achieved at risk.[7] The ban on adding flavor to these products and the limitation on the minimum purchase age are intended to help as tools to reduce the initiation of tobacco use in young people.[8]

As the tobacco industry innovates with new ways to market its products, including harnessing social media to reach young people using marketing campaigns and so-called influencers, tobacco control strategies must also evolve.[9]

A decade after the introduction of the Framework Convention on Tobacco Control (FCTC) of the World Health Organization it was the period of the fastest reduction in the prevalence of tobacco consumption by smokers in the greatest number of countries.[3,4] Brazil, Norway and Senegal, associated with Iceland, Denmark, Canada, Australia, Colombia and Costa Rica, all with prevalence reductions of more than 45%, have demonstrated the potential of this tool to significantly reduce the prevalence of tobacco use and save millions of people lives.[10]

Despite these successes, there are three worrying situations. The first concerns countries with large populations and high prevalence of smoking: China and Indonesia. In China there were 2.4 million deaths in 2019, resulting from a 57.9% increase (95%CI:26.2-101.0) in deaths attributable to smoking since 1990. In Indonesia there were 246,400 deaths in 2019, with 118% (95%CI:74.0–171.0) increase in deaths attributable to smoking since 1990.[3] Second, most countries have not

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achieved sufficient reductions in smoking prevalence to offset the demographic strength of its population growth, resulting in a constant or growing number of smokers over time.[3] And third, in many countries, including those that have previously experienced large reductions in smoking prevalence, the rate of progress has slowed, especially over the past five years.[3]

Low- and middle-income countries face the additional challenge of population growth, thus expanding their smoking population. Tobacco taxation is a highly cost-effective measure and, when combined with the progressive approach to redistributing the revenue from tobacco taxation to tobacco control programs, health care and other social support services, it can significantly reduce smoking prevalence and substantially improve population health.[10]

Smoking remains a definitive global health challenge. The current level of implementation of tobacco control policy is insufficient in many countries around the world, but it appears from the report that Brazil is doing its homework, but still has a long way to go.[3]

With more than 1 billion people smoking tobacco worldwide in 2019, the number of annual deaths, economic costs and burdens on health systems caused by smoking are sure to increase in the coming years, unless countries act aggressively based on evidence, strategies to prevent onset and stop the steady stream of new smokers.[3]

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Pneumomediastinum "through the shoulder": report of a rare case

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TO THE EDITOR:

Pneumomediastinum occurs when alveolar rupture resulting from a sudden increase in intra-alveolar pressure causes air to leak into the mediastinal space, although it can also occur with air escaping from the airways, lungs, or esophagus.[1,2] Alveolar rupture allows free air to dissect the cervical subcutaneous tissues, epidural space, pericardium, and peritoneal cavity toward and into the mediastinum.[2] Common presenting symptoms include chest pain, dyspnea, soft tissue emphysema, and crackles.[1] However, some patients are asymptomatic.[3] Pneumomediastinum is usually classified as spontaneous or secondary; the latter is also known as traumatic pneumomediastinum, the causes of which include iatrogenic causes.

Here, we report the case of a healthy, 57-year-old nonsmoking man who underwent arthroscopic surgery to repair tears of the left supraspinatus and infraspinatus tendons under general anesthesia. After the procedure, the patient developed palpable subcutaneous emphysema in the left shoulder, cervical, and infraclavicular regions. He presented with no pain, dyspnea, or hemodynamic instability. A chest CT scan revealed extensive subcutaneous emphysema of the left chest wall, extending to the upper left arm and along the entire neck, reaching the left side of the face (Figure 1).

The patient was placed on bed rest and oxygen supplementation to improve resorption of air in the mediastinum and was closely monitored. He did not undergo bronchoscopy. Nevertheless, the absence of CT findings of airway injury, the absence of previous lung disease, and the fact that the subcutaneous emphysema was clearly left-sided led us to believe that the pneumomediastinum had been caused by the arthroscopic procedure.

Arthroscopic shoulder surgery is a common procedure, with a complication rate of up to 7.9%.[4] Pneumomediastinum has been reported as a rare complication of arthroscopic shoulder surgery,[5,6] with only 8 cases reported in the literature.[6]

The exact pathogenic mechanism remains uncertain. Possible causes include general/locoregional anesthesia, endotracheal intubation, the procedure itself,[5-7] early mobilization,[5] and infectious complications following the procedure.[8]

In the case reported here, as in other similar cases, pneumomediastinum was probably procedure-related. During shoulder arthroscopy, the subacromial space is dilated by fluid pressure through the arthroscopy infusion pump. This allows good visualization of the joint while maintaining regular intra-articular pressure.[7] When the power shaver applies suction, the pressure in the subacromial space transiently decreases and becomes negative. Under this negative pressure, air can become trapped in the subacromial space. When the infusion pump generates positive pressure, it allows air to dissect into the surrounding tissues if the power shaver is momentarily turned off, causing subcutaneous emphysema.[5,7] In this context, other possible causes of pneumomediastinum include a loose junction between the solution bag and the valve, and an inflow of air through the ports.[5] The air can travel through the axillary sheath and into the prevertebral space of the neck, surrounding the trachea and esophagus.[5,7]

After exclusion of concomitant disease and after a diagnosis of pneumomediastinum is made, a conservative treatment approach is appropriate because the air in the mediastinal cavity is gradually reabsorbed by the surrounding tissue.[2,9] However, short-term patient

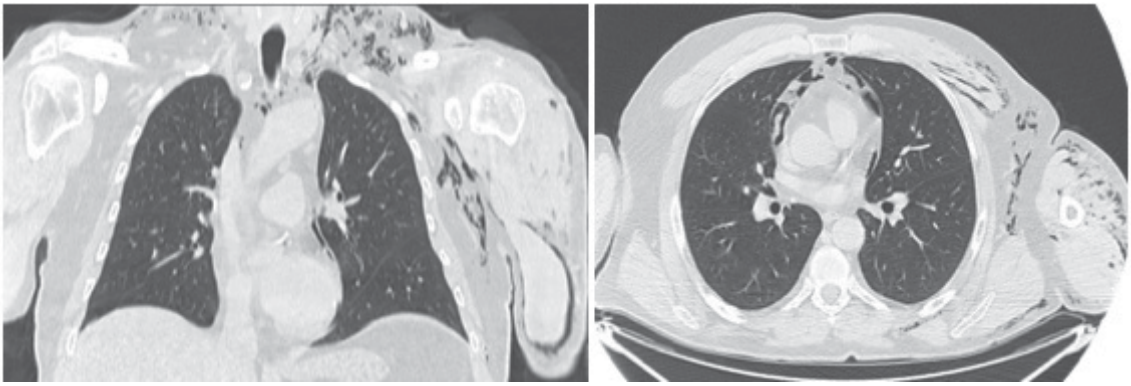

Figure 1. CT scans of the chest.

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monitoring is recommended,[10] with bed rest and cough suppression to avoid the Valsalva maneuver. The case reported here is relevant because other similar cases have been reported and because arthroscopy is a common surgical procedure.

AUTHOR CONTRIBUTIONS

CCC: drafting of the manuscript; PGF: data collection; CV and PGF: critical revision of the manuscript for important intellectual content; CCC, CV, and PGF: final approval of the version to be published.

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Lung autotransplantation for the treatment of locally advanced tumors

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TO THE EDITOR

Since the first pneumonectomy for the treatment of lung cancer, reported by Graham in 1933, and the first sleeve lobectomy for sparing lung function in 1947, by Thomas, an important discussion has been underway regarding the extension of surgical treatment and the morbimortality inherent to pneumonectomy, and the possible complications of sleeve lobectomy for the treatment of lung cancer.[1,2]

Here we describe the case of a 66-year-old man, a heavy smoker (25 pack-years and social alcoholism) with chronic obstructive pulmonary disease, who had been receiving treatment, without exacerbations within the past year, and no other comorbidities. The patient sought medical assistance due to left chest pain. Chest computed tomography (CT) showed a contralateral central mass along the course of the fissures, measuring 5 cm in its longest axis, involving the lobar bronchus of the upper lobe and contacting the bronchus of the middle lobe. Signs of invasion of the lower lobar artery and segmental branches of the middle and upper lobe were noted, with apparent hilar lymph node enlargement, without pleural effusion or other satellite lesions. Transthoracic biopsy revealed a primary Squamous Cell Carcinoma. PET-CT showed hypermetabolism of the mass (SUVmax 15.4) and hilar node (SUVmax 5.9). Brain MRI without distant metastasis. A videomediastinoscopy was performed with sampling of lymph nodes 2R, 4R, and 7, all of which were negative. Pulmonary function test showed FVC 2.75L – 73% of the predicted value, FEV1 1.64L – 55% of the predicted value, and a 0.6 FEV1/FVC ratio – 75% of the predicted value, featuring moderate obstructive ventilatory disorder. Cardiological evaluation was within the normal range, and the 6-minute walk test was > 400 meters without desaturation.

Given the extension of the tumor with bronchial invasion, the magnitude of interlobar artery involvement, and the presence of a tethering effect by the inferior pulmonary vein, double-sleeve lobectomy seemed technically unfeasible, while right pneumonectomy was a high-risk procedure due to the patient's impaired pulmonary function. We moved onto a multidisciplinary board to propose a lung autotransplant with right pneumonectomy, upper and middle lobe lobectomy, and reimplantation of the right lower lobe (RLL).

After providing consent, the patient underwent a right posterolateral thoracotomy with heparinization of the right pulmonary artery. A radical right pneumonectomy was performed, taking care to keep the pulmonary vessel stump for as long as possible to allow for a secure anastomosis. Radical lymphadenectomy of stations 2R, 4R, 7, 10R, and 11R was carried out. At the back table, antegrade and retrograde flush was conducted using pulmonary preservation solution – Perfadex® (Vitrolife; Gothenburg, Sweden), maintaining constant ventilation of the RLL. Afterward, a right upper bilobectomy was performed, with safe margins and meticulous preparation of the artery, vein, and bronchus of the RLL for reimplantation. The reimplant technique involved the following procedures: end-to-end anastomosis of the right main bronchus to the graft bronchus using polypropylene 4-0, running suture at the membranous portion and simple stitches at the cartilaginous portion; right pulmonary artery anastomosis with running polypropylene 5-0, and graft of the lower vein to the upper vein with running polypropylene 5-0; total cold ischemic time of 210 minutes. The patient was extubated in the operating room and sent to the ICU. He developed hypoxemia due to pulmonary embolism, requiring anticoagulation, and was reintubated due to pneumonia on the 9th postoperative day (POD), undergoing mechanical ventilation for 8 days. After this critical initial period, he recovered and was discharged home on 34th POD. Pathology showed invasive Squamous Cell Carcinoma stage pT3pN1 (AJCC 8th edition), with tumor-free resection margins including all critical anastomoses. He received adjuvant chemotherapy, and his follow-up was uneventful 7 months later (Figure 1).

Sleeve resections have acceptable morbidity and similar survival rates to those observed in lobectomies.[3,4] However, it is also known that pneumonectomy has higher morbimortality when compared to the two procedures (5-7% vs. 1%), especially on the right side, which is 2-fold higher than on the left on account of bronchopleural fistulae.[5,6] Indeed, despite the consolidated indication of sleeve and double-sleeve resections, which may spare pulmonary function, in widespread lesions, the gap of the bronchovascular stumps precludes an unchallenging surgery due to technical issues.[7] Therefore, in order to achieve a tension-free anastomosis and reconstruction of the bronchovascular structures, a radical pneumonectomy with *ex situ* dissection and autotransplantation of the healthy graft may be the best choice. Since the 2000s, few cases have been reported, and despite the prejudgment beyond this method and its indications, it proves effective, with no extra time or cost, except for the perfusion. Regardless of no allograft rejection, with adequate perfusion and shorter ischemic time, the complication

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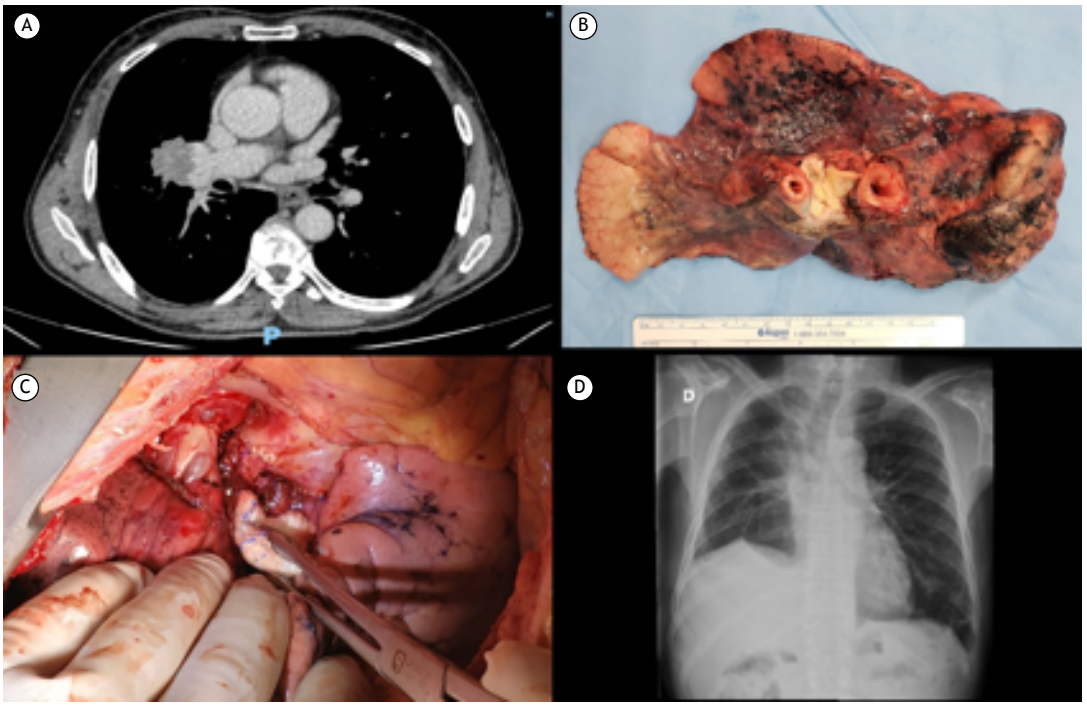

Figure 1. A: Preoperative axial tomographic section; B: Surgical resection showing intimate relationship of the tumor with the bronchovascular structures; C: Perihilar anastomosis after graft implantation; D: Late postoperative chest radiography.

of this technique is similar to double-sleeve lobectomy with lung function preservation.[8–10]

Lung sparing surgery must be a priority in locally advanced tumors and should be advocated whenever possible. However, in cases where sleeve lobectomy is impossible, lung autotransplantation is feasible and should be proposed as an alternative for patients with impaired pulmonary function. A good preoperative evaluation, surgical team expertise with stepwise meticulous preparation, and multidisciplinary approaches are cornerstones for developing a surgical program for complex cancer cases.

AUTHOR CONTRIBUTIONS

JMLTB, GLA, OGJR, BJB, and MNS: conception and planning of the study; data collection and tabulation; creation of figures; 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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An uncommon cause of miliary disease: intravesical BCG immunotherapy

Marcelo Azevedo[1], Glaúcia Zanetti[1], Edson Marchiori[1]

A 71-year-old man was admitted with a one-week history of nocturnal fever, cough, chills, and malaise. He had previously been diagnosed with superficial bladder cancer (low-grade papillary urothelial carcinoma). During post-surgical follow-up, his physicians decided to start treatment with intravesical instillation of BCG for six weeks, followed by monthly maintenance treatment for 1 year. The current symptoms of the patient appeared 1 year after treatment initiation. Chest CT demonstrated diffuse pulmonary micronodules with a random pattern (Figure 1). The patient was diagnosed with granulomatous lung disease caused by *Mycobacterium bovis*, and treatment with oral prednisolone, rifampin, isoniazid, and ethambutol was initiated, resulting in symptom improvement.

BCG immunotherapy for the treatment of *in-situ* carcinoma of the urinary bladder is the adjuvant treatment of choice. It is generally well tolerated and has no serious side effects; however, BCG may cause multisystem disease. BCG-induced pneumonitis, the pathogenesis of which may be related to *M. bovis* infection or a hypersensitivity reaction, occurs in less than 1% of patients. The lungs are the most commonly affected extra-urinary organs, presenting with diffuse interstitial disease; the most common finding is the presence of diffuse micronodules with a random pattern simulating miliary tuberculosis. This condition is treated with antitubercular medications and corticosteroids.[1-3]

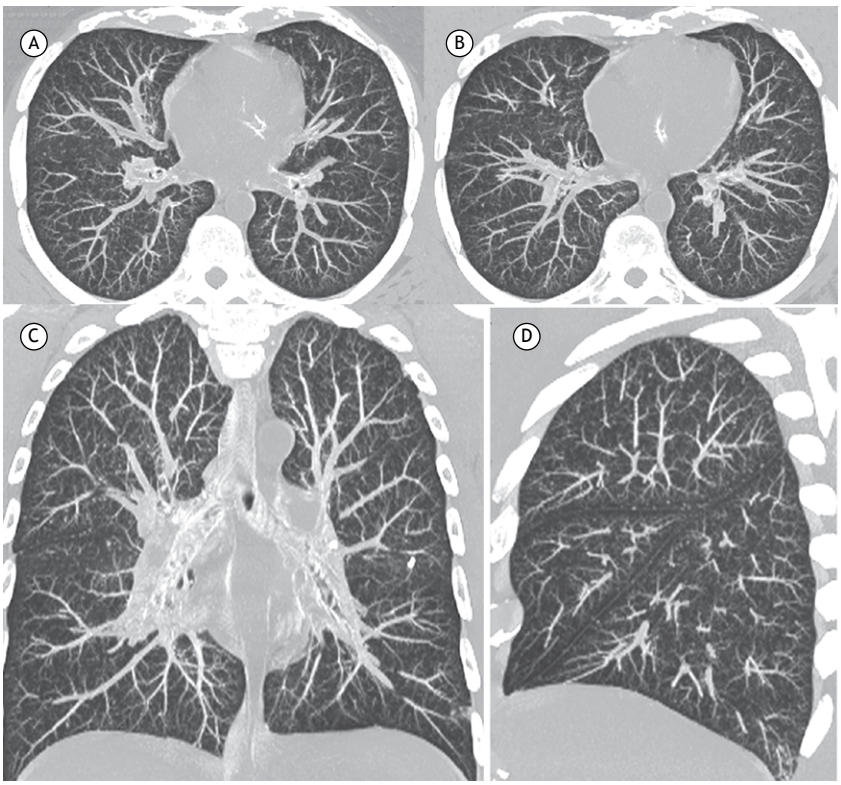

Figure 1. Axial (in A and B), coronal (in C), and sagittal (in D) reformatted CT images in maximum intensity projection show small, randomly distributed nodules. Also, note small nodules along the pulmonary fissures in C and D.

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