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HIGHLIGHT

Overprescription of short-acting β_2 agonists

Relative incidence of interstitial lung diseases in Brazil

Lung cancer screening in Brazil: recommendations from the SBCT, SBPT, and CBRDI

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
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Examining the incidence of interstitial lung disease subtypes in South America

Kirsten Nesset[1], Martin Kolb[1]

Interstitial lung disease (ILD) comprises a heterogeneous group of over 250 disorders that can be broadly categorized as being secondary to connective tissue disease (CTD-ILD), granulomatous parenchymal lung disease (hypersensitivity pneumonitis [HP] and sarcoidosis), occupational pneumoconiosis, drug-induced lung disease, familial pulmonary fibrosis, or idiopathic interstitial pneumonias. The latter group includes idiopathic pulmonary fibrosis (IPF), which is the prototypic type of progressive fibrosis which can lead to respiratory failure and death within 4-5 years. In a small subset of cases no unifying diagnosis can be confirmed, and these are often referred to as unclassifiable ILD. While many of the previous epidemiologic studies have primarily focused on IPF, regional variability in the prevalence and incidence of ILD is historically less well understood. This issue of the *Jornal Brasileiro de Pneumologia* introduces the first English language literature[1] on incidence of ILD in South America, an important contribution to our global understanding of these diseases.

Much of our current understanding of the variability of global epidemiology of ILD was recently summarized in a review that was able to comment on incidence and prevalence of the various subclassifications of ILD from North America, Europe, Asia, the Middle East, and Australia, but not South America. In North America and Europe, IPF and sarcoidosis were the most prevalent disorders, whereas in Asia a higher relative frequency of HP was observed (10.7-47.3% in India, 12.3% in Pakistan). The greatest variability was with the diagnosis of CTD-ILD, which ranged from 7.5% in Belgium to approximately one third of cases in Canada and Saudi Arabia.[2]

Until now, there has been a notable gap in the literature regarding the incidence of ILD in South America and it has been postulated that previous lack of access to CT scanning and specialized pathologist/radiologist assessment has been a contributing factor.[3] However, thanks to registry data available across six national reference centers in Brazil this is no longer the case. Using retrospective review of cases of incident ILD from this registry over six years, the authors are able to describe the relative frequency of the different ILD subtypes in Brazil for the first time. Whereas other studies have included small or single-center populations, their study[1] is strengthened by the large multicenter sample size of over 1,000 patients, assessment of atypical cases by expert multidisciplinary discussion, and a high proportion of cases with available histopathologic data. The population studied showed slight female predominance with a majority of fibrotic ILD (73.7%). The most common ILD diagnosed was CTD-ILD (26.8%) followed by HP (23.2%) and IPF (14.1%). These findings highlight important differences in the ILD population in South America; in particular, the increased incidence of CTD-ILD and HP is more similar to recent studies from India and Saudi Arabia as compared to Europe and North America.[4,5]

Whether differences in reported ILD frequencies represent true ethnic or geographic variability has been difficult to conclude. Studies using registry data are always affected by selection and referral bias, and there have been significant differences in disease classification (reflecting inconsistent or changing diagnostic criteria) and methodologies between studies. One example in this study[1] is that the authors have elected to include ILD with autoimmune features (IPAF) with CTD-ILD, which comprised 14.7% of total cases and contributed to the relatively large overall prevalence of CTD-ILD observed. Another study to have included IPAF in this category was from Saudi Arabia, who reported a similarly increased incidence of 34.8%.[5] As only a small percentage of patients with IPAF progress to a diagnosis of CTD-ILD and management is not standardized,[6] its inclusion with confirmed CTD-ILD is debatable. However, the authors justified it to emphasize that close collaboration with Rheumatology should be encouraged as their input may improve the specificity of diagnosis in this significant cohort of patients.

Similar to CTD-ILD, the incidence of HP secondary to mold and bird/feather exposure was increased in Brazil, which was attributed to housing conditions with damp indoor spaces and an increased number of captive birds being held in close proximity to humans in the region. In other regions with higher frequency of HP, such as India, it is hypothesized that mold from air coolers may also be implicated.[4] By identifying regions with increased HP and their most prevalent culprit antigens, we grow closer to being able to develop regionally specific questionnaires that can be validated and reliably used to identify relevant exposures, something that has previously been called for in the literature.[7]

In summary, establishing the incidence of ILD in Brazil is an important contribution to our global understanding of this subset of diseases and can be used both locally and internationally to inform and influence clinical practice and public health policy. Future efforts to define regional differences in ILD subtypes would benefit from standardization of diagnostic criteria and study methodology to reduce heterogeneity and better elucidate potential ethnic, geographic, and environmental risk factors for ILD.

1. Firestone Institute for Respiratory Health, Division of Respirology, McMaster University, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada.

REFERENCES

1. Matias SLK, Pereira CAC, Soares MR, Fernandes FCV, Moreira MAC, Baptista FMA, et al. Relative incidence of interstitial lung diseases in Brazil. J Bras Pneumol. 2024;50(1):e20230232.
2. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in Global Prevalence of Interstitial Lung Disease. Front Med (Lausanne). 2021;8:751181. https://doi.org/10.3389/fmed.2021.751181
3. Richeldi L, Rubin AS, Avdeev S, Udwadia ZF, Xu ZJ. Idiopathic pulmonary fibrosis in BRIC countries: the cases of Brazil, Russia, India, and China [published correction appears in BMC Med. 2021 Sep 5;19(1):220]. BMC Med. 2015;13:237. https://doi.org/10.1186/s12916-015-0495-0
4. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar, et al. Interstitial Lung Disease in India. Results of a Prospective Registry. Am J Respir Crit Care Med. 2017;195(6):801-813. https://doi.org/10.1164/rccm.201607-1484OC
5. Alhamad EH. Interstitial lung diseases in Saudi Arabia: A single-center study. Ann Thorac Med. 2013;8(1):33-37. https://doi.org/10.4103/1817-1737.105717
6. Mackintosh JA, Wells AU, Cottin V, Nicholson AG, Renzoni EA. Interstitial pneumonia with autoimmune features: challenges and controversies. Eur Respir Rev. 2021;30(162):210177. https://doi.org/10.1183/16000617.0177-2021
7. Johannson KA, Barnes H, Bellanger AP, Dalphin JC, Fernández Pérez ER, Flaherty KR, et al. Exposure Assessment Tools for Hypersensitivity Pneumonitis. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2020;17(12):1501-1509. https://doi.org/10.1513/AnnalsATS.202008-942ST

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Asthma remission

Paul M O'Byrne[1]

The term "remission" is frequently used in medicine, particularly in the management of chronic inflammatory diseases and cancer. It is defined as the reduction or disappearance of signs and symptoms of a disease. A reduction is known as a partial remission, and disappearance as a complete remission. There is an important element of the time during which the signs and symptoms have disappeared, and this duration varies with the type of the chronic disease.

Importantly, remission does not imply absence of treatment for the disease, nor is it the same as a cure; however, complete remission of evidence of the presence of some cancers over a five-year time frame is considered evidence of a cure.

Asthma is the most common chronic respiratory disease, affecting more than 350 million patients worldwide.[1] There are effective medications for asthma treatment, most notably inhaled corticosteroids (ICS), alone or together with long-acting inhaled β_2 agonists (LABA).[2] The objective of asthma treatment is to obtain asthma control. The concept of asthma control has been in use for more that 20 years. It consists of (i) absence of daytime or nighttime asthma symptoms; (ii) absence of asthma exacerbations; (iii) normal lung function; (iv) normal activities of daily living. The amount of treatment needed to achieve asthma control has been used as an indicator of asthma severity. Asthma control can be achieved in most asthma patients by using inhaled medications.

There are, however, a minority of asthma patients (7-10%) who do not achieve asthma control, even with higher doses of inhaled ICS/LABA therapy.[3] These patients have more frequent severe asthma exacerbations, often reduced lung function, and major impact on their daily lives. Up to 70% of these severe asthma patients are recognized to have persisting eosinophilic airway inflammation, which is termed T_2-high severe asthma.[3] A range of monoclonal antibodies have been developed which target specific proteins associated with T_2-high asthma, which are collectively known as asthma biologics. These are antibodies which bind to IL-5 (mepolizumab and reslizumab)[4,5]; to the IL-5 receptor α (benralizumab)[6]; to the IL-4 receptor α (dupilumab)[7]; to IgE (omalizumab)[8]; or to thymic stromal lymphopoietin (tezepelumab).[9,10] Each of these biologics improves asthma control in severe T_2-high asthma by reducing exacerbations, improving symptoms, and improving lung function. Several asthma biologics have also been demonstrated to be oral corticosteroid sparing.[11-13]

A concept has been proposed that, by blocking cytokines important in the pathogenesis of asthma, biologics may have a greater likelihood of inducing asthma remission than conventional therapies.[14] This is not an unrealistic hypothesis. There are known clinical situations where an asthma cure has occurred. A cure would be identified not only by absence of symptoms, but also by the absence of the characteristic inflammatory biomarkers and physiological abnormalities of asthma, particularly airway hyperresponsiveness. This has been described in patients with occupational asthma to western red cedar; in these cases, early removal of the patients from the workplace has resulted in cure.[15] In addition, many children with asthma have a complete remission of their symptoms during adolescence,[16] although some have a recurrence of asthma later in life.

With regards to the use of asthma biologics, most studies have identified patients who have a greater clinical response, as measured by standard clinical outcomes, than the mean results for the study group. These patients have been called "super-responders."[17] While the concept of remission is different, neither the definition nor the period of remission has been agreed and differs in studies which have evaluated the benefits of asthma biologics in inducing partial remission (Table 1), and, not surprisingly, the percentage of patients considered to be in remission varies from 15% to 41%.[18-21] The most consistent features of partial remission in these studies are symptom control, the absence of need for oral corticosteroids, and the absence of asthma exacerbations for at least 1 year.

There is a high likelihood that the term "asthma remission" will become more widely used in studies examining the efficacy of asthma biologics. It will be important to come to a consensus on defining the term, particularly as comparisons will be made (often inappropriate) between studies where remission has been a clinical outcome. Several efforts have been made to provide a definition,[22-24] but have not yet become widely accepted. This definition of a complete asthma remission should include absence of asthma symptoms, absence of exacerbations and of the need for oral corticosteroids, and maintenance of the patients' best FEV_1 values, with no evidence of variability. These benefits should be maintained for at least 1 year. Occasional symptoms, the level of which is yet to be defined, and particularly if caused by external stimuli, such as exercise or atmospheric pollutants, may be acceptable to define a partial asthma remission.

While there are benefits in focusing on asthma remission as a clinical outcome, there are both unanswered questions and risks. The absence of a widely agreed definition has already been discussed, but there is also no information about the duration of time that a patient

1. Firestone Institute for Respiratory Health and the Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Table 1. Definitions of asthma remission in patients on asthma biologics.

Variable	Menzies-Gow et al.[21]	Pavord et al.[20]	Oishi et al.[19]	McDowell et al.[18]
ACQ-5/6	< 1.5 or ≤ 0.75	N/A	< 1.5	< 1.5
ACT	N/A	> 20	N/A	N/A
FEV_1	≥ 100 mL improvement	N/A	> 80% predicted	Above LLN or < 100 mL baseline value
OCS use	Zero	Zero	Zero	Zero
Asthma exacerbations	Zero	Zero	Zero	N/A
Duration	6 months	1 year	1 year	1 year
Patients with remission	15-23%	41%	31.5%	18%

ACQ: asthma control questionnaire; ACT: asthma control test; OCS: oral corticosteroids; and LLN: lower limit of normal.

should remain on an asthma biologic once remission has been achieved or about the risks of recurrence of asthma symptoms if the biologic is discontinued. Also, if remission becomes a widely accepted clinical outcome for patients on asthma biologics, and a patient does not achieve remission while on one biologic, there will be the temptation to try another, and the benefits of this to patients has not been studied yet.

REFERENCES

1. Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J. 2020;56(6):2002094. https://doi.org/10.1183/13993003.02094-2020
2. Global Initiative for Asthma [homepage on the internet]. Bethesda: Global Initiative for Asthma; c2023 [cited 2024 Jan 2]. Global Strategy for Asthma Management and Prevention (2023 update). Available from: http://www.ginasthma.org
3. Chung KF, Wenzel S; European Respiratory Society/American Thoracic Society Severe Asthma International Guidelines Task Force. From the authors: International European Respiratory Society/American Thoracic Society guidelines on severe asthma. Eur Respir J. 2014;44(5):1378-1379. https://doi.org/10.1183/09031936.00120714
4. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma [published correction appears in N Engl J Med. 2015 Apr 30;372(18):1777]. N Engl J Med. 2014;371(13):1198-1207. https://doi.org/10.1056/NEJMoa1403290
5. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10):1125-1132. https://doi.org/10.1164/rccm.201103-0396OC
6. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-890. https://doi.org/10.1016/S2213-2600(14)70201-2
7. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med. 2013;368(26):2455-2466. https://doi.org/10.1056/NEJMoa1304048
8. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001;108(2):184-190. https://doi.org/10.1067/mai.2001.117880
9. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014;370(22):2102-2110. https://doi.org/10.1056/NEJMoa1402895
10. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al. Tezepelumab in Adults with Uncontrolled Asthma [published correction appears in N Engl J Med. 2019 May 23;380(21):2082]. N Engl J Med. 2017;377(10):936-946. https://doi.org/10.1056/NEJMoa1704064
11. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009;360(10):985-993. https://doi.org/10.1056/NEJMoa0805435
12. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P,et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017;376(25):2448-2458. https://doi.org/10.1056/NEJMoa1703501
13. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. 2018;378(26):2475-2485. https://doi.org/10.1056/NEJMoa1804093
14. Upham JW, James AL. Remission of asthma: The next therapeutic frontier?. Pharmacol Ther. 2011;130(1):38-45. https://doi.org/10.1016/j.pharmthera.2011.01.002
15. Malo JL, Chan-Yeung M. Occupational asthma. J Allergy Clin Immunol. 2001;108(3):317-328. https://doi.org/10.1067/mai.2001.116432
16. Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koëter GH, et al. Childhood factors associated with asthma remission after 30 year follow up. Thorax. 2004;59(11):925-929. https://doi.org/10.1136/thx.2003.016246
17. Upham JW, Le Lievre C, Jackson DJ, Masoli M, Wechsler ME, Price DB; et al. Defining a Severe Asthma Super-Responder: Findings from a Delphi Process. J Allergy Clin Immunol Pract. 2021;9(11):3997-4004. https://doi.org/10.1016/j.jaip.2021.06.041
18. McDowell PJ, McDowell R, Busby J, Eastwood MC, Patel PH, Jackson DJ, et al. Clinical remission in severe asthma with biologic therapy: an analysis from the UK Severe Asthma Registry. Eur Respir J. 2023;62(6):2300819. https://doi.org/10.1183/13993003.00819-2023
19. Oishi K, Hamada K, Murata Y, Matsuda K, Ohata S, Yamaji Y, et al. A Real-World Study of Achievement Rate and Predictive Factors of Clinical and Deep Remission to Biologics in Patients with Severe Asthma. J Clin Med. 2023;12(8):2900. https://doi.org/10.3390/jcm12082900
20. Pavord I, Gardiner F, Heaney LG, Domingo C, Price RG, Pullan A, et al. Remission outcomes in severe eosinophilic asthma with mepolizumab therapy: Analysis of the REDES study. Front Immunol. 2023;14:1150162. https://doi.org/10.3389/fimmu.2023.1150162
21. Menzies-Gow A, Hoyte FL, Price DB, Cohen D, Barker P, Kreindler J, et al. Clinical Remission in Severe Asthma: A Pooled Post Hoc Analysis of the Patient Journey with Benralizumab. Adv Ther. 2022;39(5):2065-2084. https://doi.org/10.1007/s12325-022-02098-1
22. Thomas D, McDonald VM, Pavord ID, Gibson PG. Asthma remission: what is it and how can it be achieved?. Eur Respir J. 2022;60(5):2102583. https://doi.org/10.1183/13993003.02583-2021
23. Lommatzsch M, Buhl R, Canonica GW, Ribas CD, Nagase H, Brusselle GG, et al. Pioneering a paradigm shift in asthma management: remission as a treatment goal. Lancet Respir Med. Epub online ahead of print. https://doi.org/10.1016/S2213-2600(23)00415-0
24. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. J Allergy Clin Immunol. 2020;145(3):757-765. https://doi.org/10.1016/j.jaci.2019.12.006

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One step forward in understanding sleep in hypersensitivity pneumonitis patients

Paulo Mateus Madureira Soares Mariano[1], Pedro Rodrigues Genta[1]

In the previous issue of the *Jornal Brasileiro de Pneumologia*, Martins et al.[1] compared the prevalence of obstructive sleep apnea (OSA), patterns of nocturnal desaturation, sleep distribution, and sleep efficiency between patients with chronic hypersensitivity pneumonitis (HP) and controls. The accuracy of questionnaires for OSA detection was also tested. The study included 40 patients diagnosed with chronic HP and 80 controls whose spirometry results were within normal parameters. The selection of chronic HP patients followed specific criteria established by Salisbury et al.,[2] with matching controls based on sex, age, and BMI. We commend the authors for their study, given the scarcity of data on OSA in chronic HP patients.

Previous studies have reported a high prevalence of OSA in patients with interstitial lung disease (ILD), ranging from 68% to 88%.[3-5] Small observational studies have shown a similar prevalence of OSA in patients with ILD.[6] The high prevalence of OSA among ILD patients can be explained by the also high prevalence of OSA in adults, especially in the elderly.[7] In addition, the potential decrease in lung volume caused by the ILD can increase upper airway collapsibility due to the reduction of the tracheal tug on the pharynx.[8] The association between ILD and OSA is potentially harmful: previous evidence has shown a negative impact on nocturnal desaturation and survival.[9]

The main finding in the study by Martins et al.[1] was that the prevalence of OSA in patients with chronic HP was similar to that in matched control subjects. Another relevant finding was the inaccuracy of screening questionnaires for OSA among individuals with chronic HP. Additionally, the study revealed that sleep quality was poorer in chronic HP patients than in controls. However, it is not possible to estimate whether impairment of sleep quality was due to the underlying lung disease or OSA. Future studies should compare chronic HP patients with controls, including patients with and without OSA to explore the potential contribution of each disorder on sleep quality impairment. The authors also showed a higher percentage of total sleep time with SpO_2 below 90% in the chronic HP group when compared with the control group, which may potentially increase morbidity.

The authors highlighted several limitations. The sample size was relatively small, and participants were recruited from a single center, a limitation that restricts the generalizability of the results and their representation in different clinical settings. The study also excluded patients in more advanced stages of chronic HP, which might have influenced the prevalence of OSA and the interpretation of test results. Another limitation was the lack of a detailed description of spirometric results in the control group. Despite these limitations, the findings of the study by Martins et al.[1] are important because they demonstrate a complex and not yet fully understood relationship between ILD, particularly chronic HP, and OSA. The study underscores the high prevalence of OSA in patients with chronic HP, emphasizing the need for a more in-depth investigation into quality of sleep and nocturnal oxygenation in these patients. Additionally, similarly to other studies, it highlights the ineffectiveness of sleep questionnaires in accurately identifying OSA in this population.[4,10,11] Despite the high prevalence, systematic screening for OSA among patients with chronic HP is not currently justified. Studies assessing the impact of OSA treatment in individuals with chronic HP may, in the future, determine the utility of systematic OSA screening.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the writing and reviewing of the manuscript and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Martins RB, Bittencourt LRA, Botelho AB, Resende ACL, Gomes PS, Tufik S, et al. Sleep parameters in patients with chronic hypersensitivity pneumonitis: a case-control study. J Bras Pneumol. 2023;49(5):e20230036. https://doi.org/10.36416/1806-3756/e20230036
2. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and Treatment of Fibrotic Hypersensitivity Pneumonia. Where We Stand and Where We Need to Go. Am J Respir Crit Care Med. 2017;196(6):690-699. https://doi.org/10.1164/rccm.201608-1675PP
3. Pihtili A, Bingol Z, Kiyan E, Cuhadaroglu C, Issever H, Gulbaran Z. Obstructive sleep apnea is common in patients with interstitial lung disease. Sleep Breath. 2013;17(4):1281-1288. https://doi.org/10.1007/s11325-013-0834-3
4. Lancaster LH, Mason WR, Parnell JA, Rice TW, Loyd JE, Milstone AP, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest. 2009;136(3):772-778. https://doi.org/10.1378/chest.08-2776
5. Mermigkis C, Stagaki E, Tryfon S, Schiza S, Amfilochiou A, Polychronopoulos V, et al. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis?. Sleep Breath. 2010;14(4):387-390. https://doi.org/10.1007/s11325-010-0336-5

1. Laboratório do Sono – LIM 63 – Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Universidade de São Paulo, São Paulo (SP) Brasil.

6. Pereira N, Cardoso AV, Mota PC, Santos AC, Melo N, Morais A, et al. Predictive factors of obstructive sleep apnoea in patients with fibrotic lung diseases. Sleep Med. 2019;56:123-127. https://doi.org/10.1016/j.sleep.2019.01.020
7. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-446. https://doi.org/10.1016/j.sleep.2009.10.005
8. Khor YH, Ryerson CJ, Landry SA, Howard ME, Churchward TJ, Edwards BA, et al. Interstitial lung disease and obstructive sleep apnea. Sleep Med Rev. 2021;58:101442. https://doi.org/10.1016/j.smrv.2021.101442
9. Kolilekas L, Manali E, Vlami KA, Lyberopoulos P, Triantafillidou C, Kagouridis K, et al. Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. J Clin Sleep Med. 2013;9(6):593-601. https://doi.org/10.5664/jcsm.2758
10. Duarte RLM, Togeiro SMGP, Palombini LO, Rizzatti FPG, Fagondes SC, Magalhães-da-Silveira FJ, et al. Brazilian Thoracic Association Consensus on Sleep-disordered Breathing. J Bras Pneumol. 2022;48(4):e20220106. https://doi.org/10.36416/1806-3756/e20220106
11. Zhang XL, Dai HP, Zhang H, Gao B, Zhang L, Han T, et al. Obstructive Obstructive Sleep Apnea in Patients With Fibrotic Interstitial Lung Disease and COPD. J Clin Sleep Med. 2019;15(12):1807-1815. https://doi.org/10.5664/jcsm.8090

Arteriovenous malformation

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

A 37-year-old woman presented with a three-day history of cough and fever. A chest X-ray showed a nodule at the right lung base. CT confirmed the finding and also showed vessels intimately related to the nodule (Figure 1). The final diagnosis was arteriovenous malformation.

A pulmonary nodule is defined as a focal rounded opacity measuring up to 3 cm in diameter. An opacity greater than 3 cm in diameter is called a mass, and an opacity less than 1 cm in diameter is called a small nodule. Pulmonary nodules may be solitary or multiple, and they may have soft- tissue, fluid, calcium, air (cavitated nodules), fat, or ground-glass density. A solitary pulmonary nodule is a frequent problem for radiologists and pulmonologists, given the possibility of numerous benign and malignant etiologies. The detection of a solitary pulmonary nodule on imaging is always worrisome because one of its most common etiologies is bronchogenic carcinoma. CT is extremely important in evaluating the morphological features of such a nodule in search of characteristics that may suggest benignity. Some criteria that are suggestive of benignity include evidence of nodule stability for more than 2 years, presence of fat, or presence of specific patterns of calcification.[1]

Pulmonary arteriovenous malformations (PAVMs) are abnormal connections between the pulmonary artery and pulmonary vein, bypassing the normal capillary bed, causing a right-to-left shunt. The majority of PAVMs are associated with hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu syndrome), an autosomal dominant disorder that is characterized by arteriovenous malformations in multiple tissues and organs. PAVMs can be divided into simple and complex depending on the number of feeding pulmonary arteries. PAVMs may be asymptomatic or present with symptoms of dyspnea secondary to hypoxemia, sequelae of paradoxal embolization, or rupture. Epistaxis is the most common symptom, seen in nearly all adults with hereditary hemorrhagic telangiectasia. CT is the method of choice for diagnosing PAVMs. The classic CT feature of a PAVM is that of a well-defined peripheral nodule, which can be rounded or multilobulated, with one feeding artery and one or more draining veins. The draining veins are typically larger than the feeding arteries. Maximum intensity projection and three-dimensional reconstructions can help delineate the vascular anatomy of such lesions.[2,3]

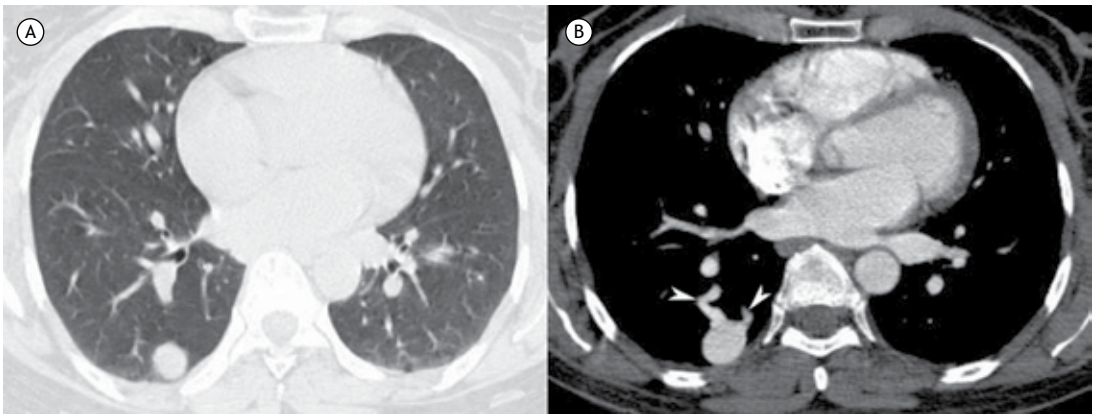

Figure 1. Chest CT displayed in lung (A) and mediastinal (B) windows shows a well-circumscribed nodule in the right lower lobe. In B, contrast enhancement reveals the presence of two vascular outlines (arrowheads) intimately related to the nodule, which correspond to the feeding artery and the draining vein.

REFERENCES

1. Webb WR, Muller NL, Naidich DP, editors. High-resolution CT of the lung. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
2. Kaufman CS, McDonald J, Balch H, Whitehead K. Pulmonary Arteriovenous Malformations: What the Interventional Radiologist Should Know. Semin Intervent Radiol. 2022;39(3):261-270. https://doi.org/10.1055/s-0042-1751260
3. Lee HN, Hyun D. Pulmonary Arteriovenous Malformation and Its Vascular Mimickers. Korean J Radiol. 2022;23(2):202-217. https://doi.org/10.3348/kjr.2021.0417

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Randomized controlled trials: advantages and pitfalls when studying causality

Diego Caruso[1,2], Juliana C Ferreira[2,3]

PRACTICAL SCENARIO

A pharmaceutical company has developed a new drug to improve asthma control and they are asking a respected team of investigators to design a study to compare "betteraline" (new drug) with "normalraline" (usual care). The investigators believe that the best design should be a randomized controlled trial (RCT) comparing both drugs and measuring the improvement in FEV_1 after three months of treatment as the main outcome. However, they are worried about costs, time commitment, and the need for an organized team to minimize follow-up losses, as well as about the logistics to measure the primary outcome. They wonder what pros and cons of performing an RCT are in this case.

In clinical and epidemiological research, analytical studies aim to assess the potential cause-effect association between an intervention and an outcome to ensure that causation is the best possible explanation among all available options.

To establish causation, the research question we would like to answer is: what would the outcome be if patients received an experimental intervention (factual scenario) compared with what would have happened if the same patients had received a control treatment, at the same moment of their lives, under identical conditions (counterfactual scenario)? Because we cannot test that in real life, the best substitute is to randomly select "similar" patients to receive either the intervention or the control and to compare outcomes. The outcome of the control group is the counterfactual scenario.[1] Although not perfect, this model served as the central concept inspiring the inception of randomized experiments and their statistical inference by Ronald Fisher circa 1920.

ADVANTAGES OF RCTS

RCT is a robust design because participants are randomly assigned to receive the intervention or control, which ensures that both known and unknown potential confounders are balanced at baseline in the two (or more) study groups. This process is achieved in two steps. First, the generation of a random list; second, allocation concealment, which is a procedure to prevent investigators from knowing to which group the next patient will be assigned. There are a few ways to do this, such as using sealed opaque envelopes or using digital automated response systems accessed by phone or over the Internet.

Any attempt to manipulate the process disrupts the balance that we are trying to achieve. Another advantage of RCTs is that measurement of variables during the study is prospective and ensures that all participants have measurements taken in the same manner throughout the study, avoiding information bias, minimizing missing data, and increasing internal validity.

Masking, when possible, is another advantage of RCTs. The participants, the researchers who follow the patients during the study, the researchers who are responsible for defining whether or not the participants experienced the outcome, and/or the statistician who analyzes the data may be prevented from knowing the assignment of each participant in order to minimize bias.

Performing an RCT requires a lot of preparation, with a carefully designed study protocol, a manual of procedures (for example, specific instructions to perform spirometry), a team, and an experienced leader. That takes time and money; therefore, a realistic schedule and budget are essential.

IMPORTANT CONSIDERATIONS AND PITFALLS

Participants in an RCT are not selected at random from the population of interest. They are usually referred by their doctors or self-referred by seeing advertisements or receiving recommendations from other patients, which might affect generalizability. In addition, the wonders of randomization are at the heart of RCTs, but like any vital organ, it can be affected by certain conditions:

- Crossover: patients who are assigned to one of the study arms but, due to unexpected reasons, receive the treatment of the other study arm. For instance, participants assigned to the intervention group obtain inhalers containing "normalraline" at a pharmacy.
- Nonadherence: some participants may not adhere to the assigned treatment. In our example, a patient may decide to stop using his/her asthma inhalers. If this proportion is high, or if it occurs more frequently in one arm than in another, it becomes a potential bias.
- Loss to follow-up: if a participant drops out of the study and cannot be contacted, it cannot be determined whether they experienced the study outcome or not, affecting the interpretation of the results.[2]

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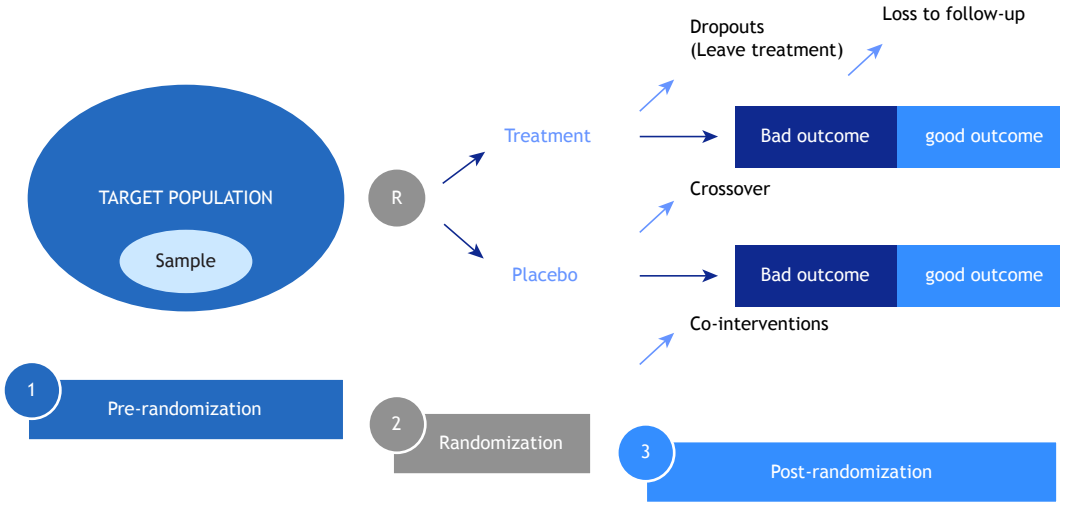

Figure 1. Framework and potential pitfalls in randomized clinical trials. Loss to follow up, dropout, co-interventions and crossover can happen in either of the study arms. R: randomization.

- Co-interventions: when participants receive interventions other than the main intervention, it may be difficult to know whether to attribute the benefit to the study intervention or to the co-intervention. In our example, the addition of corticosteroids to achieve asthma control is a co-intervention.

The investigators have decided to perform an RCT to test if "betteraline" is superior to usual care to treat asthma, because RCT is the most robust design to determine causality if all premises are met. To obtain valid results, the study will need careful planning, time, resources, and a dedicated team.

REFERENCES

1. Höfler M. Causal inference based on counterfactuals. BMC Med Res Methodol. 2005;5:28. https://doi.org/10.1186/1471-2288-5-28
2. Bell ML, Kenward MG, Fairclough DL, Horton NJ. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ. 2013;346:e8668. https://doi.org/10.1136/bmj.e8668

Role of the pulmonary function laboratory in investigating diaphragm dysfunction

Leticia Zumpano Cardenas[1], Pauliane Vieira Santana[2,3], André Luís Pereira de Albuquerque[3]

OVERVIEW

A previously healthy 33-year-old woman underwent left upper lobe segmentectomy for resection of a malignant mediastinal mesenchymal tumor. The surgery was complicated by an injury to the subclavian artery, hemostasis being achieved by opening the pericardium. The postoperative period was uneventful, and the patient was discharged from the ICU. However, she was readmitted to the ICU on postoperative day 5 because of respiratory failure, which was managed with continuous noninvasive ventilation (NIV). Further evaluation ruled out pulmonary congestion, infection, and thromboembolism. A chest X-ray showed an elevated left diaphragm, raising the suspicion of diaphragm dysfunction (DD). This suspicion was corroborated by extensive complementary evaluations,[1,2] including the following:

1. Pulmonary function testing (PFT) disclosed a restrictive pattern (a substantial drop in FVC and FEV_1). Unfortunately, PFT was not performed in the supine position.
2. Reduced inspiratory muscle strength on volitional tests (reduced MIP and sniff nasal inspiratory pressure) and nonvolitional tests (significantly reduced left twitch transdiaphragmatic pressure [TwPdi] but only slightly reduced right TwPdi), together with a paradoxical drop in gastric pressure during inspiration.
3. Increased recruitment of extradiaphragmatic inspiratory muscles (the scalene and sternocleidomastoid muscles), as assessed by surface electromyography.
4. Thoracoabdominal asynchrony (a phase angle of 180° indicating a paradoxical pattern), as assessed by respiratory inductance plethysmography.

Diaphragm ultrasound (DUS) confirmed the suspicion of DD. DUS showed markedly reduced left diaphragm mobility (during quiet and deep breathing), including paradoxical motion during sniffing. Yet, the left diaphragm was thin (reduced thickness), with reduced inspiratory thickening. The right diaphragm showed slightly reduced deep breathing motion, although thickness and thickening remained unaltered.[3]

CASE SUMMARY

Our patient had DD caused by bilateral traumatic injury to the phrenic nerve during open-heart surgery, DD being more severe on the left side. Dyspnea was relieved by NIV and can be explained by bilateral DD, given that unilateral DD can be asymptomatic. The fact that the patient was progressively weaned off of NIV suggested recovery of diaphragm function.

Phrenic nerve dysfunction has been described in open-heart surgery, being caused by hypothermia (topical cardiac cooling), mechanical stretching of the phrenic nerve by the sternal retractor, or a combination of the two. Phrenic nerve palsy is an uncommon complication after cardiac surgery, usually affecting only the left phrenic nerve and resolving completely in almost all cases.[4]

CLINICAL MESSAGES

DD remains underdiagnosed because of its nonspecific presentation and the difficulty in diagnosing it. Once DD is suspected, ancillary tests can be ordered to confirm it or rule it out.[2]

Unexplained dyspnea (particularly orthopnea), an elevated diaphragm on imaging, a restrictive pattern on PFT, and reduced MIP may raise the suspicion of DD. Diagnostic tests for DD include surface electromyography, respiratory inductance plethysmography, and measurement of TwPdi; however, these are largely unavailable, with measurement of TwPdi having the additional disadvantage of being an invasive test.[2] DUS, on the other hand, has many advantages, including its availability, its repeatability, and its being a noninvasive test.[5]

The following DUS findings can help confirm a diagnosis of DD, suggesting diaphragmatic paralysis[5]:

- absent mobility during quiet and deep breathing, as well as absent mobility or paradoxical motion during sniffing
- reduced diaphragm thickness (a thin, atrophic diaphragm), as well as absent diaphragm inspiratory thickening
- Normal diaphragm thickness in the presence of reduced diaphragm thickening suggests acute or subacute diaphragmatic paralysis.

The following DUS findings are diagnostic of diaphragm weakness:

- reduced diaphragm mobility and thickness, as well as reduced diaphragm inspiratory thickening (lower than the lower limit of normal in healthy individuals, sex and body position being taken into account)

AUTHOR CONTRIBUTIONS

The authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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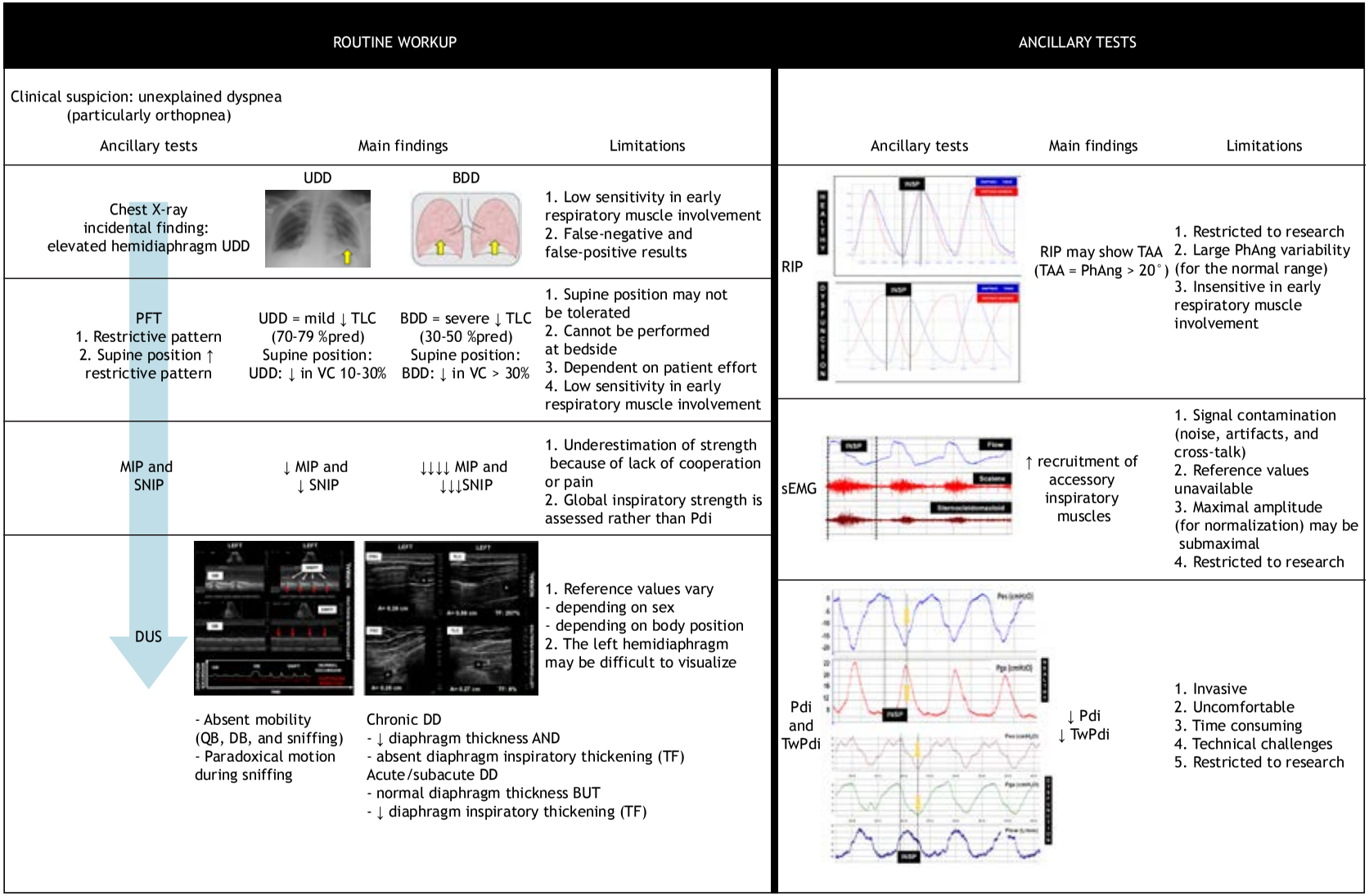

Figure 1. Flow chart of workup of diaphragm dysfunction (DD). UDD: unilateral DD; BDD: bilateral DD; PFT: pulmonary function testing; SNIP: sniff nasal inspiratory pressure; DUS: diaphragm ultrasound; QB: quiet breathing; DB: deep breathing; TF: thickening fraction; RIP: respiratory inductance plethysmography; TAA: thoracoabdominal asynchrony; PhAng: phase angle; sEMG: surface electromyography; Pdi: transdiaphragmatic pressure; and TwPdi: twitch Pdi.

REFERENCES

1. Caruso P, Albuquerque AL, Santana PV, Cardenas LZ, Ferreira JG, Prina E, et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. J Bras Pneumol. 2015;41(2):110-123. https://doi.org/10.1590/S1806-37132015000004474
2. Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M, et al. ERS statement on respiratory muscle testing at rest and during exercise. Eur Resp J. 2019;53(6):1801214. https://doi.org/10.1183/13993003.01214-2018
3. Caleffi-Pereira M, Pletsch-Assunção R, Cardenas LZ, Santana PV, Ferreira JG, Iamonti VC, et al. Unilateral diaphragm paralysis: a dysfunction restricted not just to one hemidiaphragm. BMC Pulm Med. 2018;18(1):126. https://doi.org/10.1186/s12890-018-0698-1
4. Aguirre VJ, Sinha P, Zimmet A, Lee GA, Kwa L, Rosenfeldt F. Phrenic nerve injury during cardiac surgery: mechanisms, management and prevention. Heart Lung Circ. 2013;22(11):895-902. https://doi.org/10.1016/j.hlc.2013.06.010
5. Santana PV, Cardenas LZ, Albuquerque ALP, Carvalho CRR, Caruso P. Diaphragmatic ultrasound: a review of its methodological aspects and clinical uses. J Bras Pneumol. 2020;46(6):e20200064. https://doi.org/10.36416/1806-3756/e20200064

Diagnosis and treatment of asthma in childhood: an overview of guidelines

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Asthma is the most common chronic respiratory condition of childhood worldwide, with approximately 15% of children and young people affected.[1] This review provides a concise summary of pediatric asthma diagnosis and management, benefiting health care providers in diverse child health settings.

DIAGNOSING ASTHMA IN CHILDREN

In practice, diagnosis of asthma should be established by considering characteristic symptom patterns. Asthma is distinguished by fluctuating symptoms, which may include wheezing, dyspnea, chest tightness, and cough. It is also characterized by variable limitation in expiratory airflow. Both symptoms and severity typically change over time.[1] The variations are often triggered by factors such as exercise, aeroallergens, and particularly viral respiratory infections, which may cause episodic exacerbations that can be severe or even life-threatening.[1] Other factors that support the diagnosis of asthma are respiratory symptoms that worsen at night or on waking.[2] In addition to the characteristic clinical presentation, patients with asthma often have a personal history of atopic dermatitis, or allergic rhinitis, and/or a family history of allergic diseases.

The diagnosis is established by identifying the clinical pattern of respiratory symptoms associated with variable expiratory airflow limitation, confirmed by expiratory airflow limitation through spirometry, showing reduced FEV_1 and/or FEV_1/FVC ratio (< 0,9 in children), and excessive variability in lung function, usually demonstrated by positive bronchodilator responsiveness (increase in FEV_1 from baseline by > 12% of predicted values).[2]

DIFFERENTIAL DIAGNOSIS

The most common differential diagnoses and their distinguishing symptoms from asthma in children are as follows: cystic fibrosis[3] (clubbing, family history of cystic fibrosis, gastrointestinal symptoms); primary ciliary dyskenesia (symptoms present from birth, persistent cough, chronic nasal symptoms); bronchiectasis[4,5] (persistent productive cough, finger clubbing); structural abnormality[5] (no variation in wheezing); and vocal cord dysfunction[5] (stridor, exercise-induced respiratory noise).

MANAGEMENT OF SEVERE EXACERBATIONS

Severe exacerbations represent an acute or subacute worsening of symptoms and lung function from the patient's usual status, or, in some cases, a patient may present them for the first time during an exacerbation. The aim of this management is to relieve bronchial airflow obstruction and hypoxemia rapidly, address the underlying inflammatory pathophysiology, and prevent relapse. The following procedures should be followed in all ER settings[1]:

- Evaluate the severity of exacerbation based on dyspnea, respiratory rate, and oxygen saturation; initiate treatment with short-acting β_2 agonist (SABA) and oxygen therapy; and adhere to infection control measures.[1]
- Administrate SABA repeatedly; for most patients, by pressurized metered-dose inhaler and spacer. The patient should be monitored regarding clinical response and oxygen saturation after 1 h.
- Prescribe systemic corticosteroids in severe exacerbations. Intravenous magnesium sulfate should be considered for patients with severe exacerbations unresponsive to initial treatment.[1]
- If there are signs of severe exacerbation, or if the patient exhibits drowsiness, confusion, or a silent chest, promptly transfer him/her to an acute care facility or to an ICU. During the transportation, use inhaled SABA and ipratropium bromide, oxygen therapy, and systemic corticosteroids.[1]

Evidence does not support the routine use of antibiotics in the treatment of acute asthma exacerbations unless there is evidence of bacterial lung infection (e.g. high and persistent fever or radiologic evidence of bacterial pneumonia).[1] Similarly, routine chest X-ray is not recommended unless there are physical signs suggestive of pneumothorax, bacterial pneumonia, or inhaled foreign body.[3]

MAINTENANCE THERAPIES

The main objectives of maintenance therapy are to control daily symptoms in order to minimize the risk of exacerbations and improve lung function. The evaluation of these issues must be made objectively and periodically, using clinical tools such as the GINA asthma control questionnaire or the asthma control test, which evaluates asthma control retrospectively within

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AGE	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
<6 years	Consider intermittent or daily low dose ics	Daily low dose ICS	Double "low dose" ICS	Continue controller and refer for specialist assessment	
6-11 years	Low dose ics whenever saba taken	Daily low dose inhaled ICS	Low dose ics-Laba, or medium dose ics, or very low dose ICS-formoterol mart	Medium dose ICS-laba, or low dose ICS-formoterol mart. Refer for expert advice	Refer for phenotypic Assessment ± higher dose ics-laba or add-on therapy, e.g.Anti-IgE, anti-IL4Ra, anti-IL-5
>12 years	As-needed-only low dose ICS-formoterol		Low dose maintenance ICS-formoterol	Medium dose Maintenance ICS-Formoterol	Add-on lama.refer for Assessment of phenotype. Consider high dose Maintenance ICS-LABA ± Anti-lgE, anti-IL4Ra, anti-IL-5
Managing exacerbations (Children and Adults)	Inhaled albuterol is the usual bronchodilator for acute asthma management. For mild to moderate exacerbations, repeated administration of inhaled SABA (4-10 puffs every 20 minutes for the first hour) help to achieve rapid reversal of airflow limitation. After the first hour, the dose of SABA required varies from 4-10 puffs every 3-4 hours up to 6-10 puffs every 1-2 hours, or more often.				

Figure 1. Summary framework for asthma maintenance treatment, separated by age and steps, followed by a summary of exacerbation management. ICS: inhaled corticosteroids; SABA: short-acting β_2 agonist; LABA: long-acting β_2 agonist ; and LAMA: long-acting muscarinic antagonist. Based on Carvalho-Pinto et al.[7]

four weeks, in every clinical visit, and assessing lung function once or twice a year.[6,7] Maintenance therapies follow national and international recommendations based on steps (Figure 1) as follows:

- For children aged 6 years and younger, those who do not have frequent asthma symptoms that justify the use of a daily controller often fall into step 1. From step 2 onward, the use of inhaled corticosteroids (ICS) is recommended, and the ICS dose increases as steps move up. In step 4, a specialist evaluation becomes necessary.[1]
- For children aged 6-11, the preferred treatment in step 1 consists of using intermittent low-dose ICS whenever SABA is administered. In step 2, the patient requires low-dose ICS on a daily basis. In step 3, the preferred treatment is low-dose ICS + long-acting β_2 agonist (LABA), with medium-dose ICS as an alternative therapy. In step 4, medium-dose ICS + LABA is the preferred choice, followed by referral to a specialist. Also, a long-acting muscarinic antagonist (LAMA) may be used as add-on therapy for patients in step 4. In step 5, the patient requires higher doses of ICS + LABA or a third add-on medication, requiring the evaluation by a specialist. Biologics such as anti-IgE (omalizumab), anti-IL4R (dupilumab), and anti-IL-5 (mepolizumab) may be used in patients with severe asthma.
- For patients aged 12 years and older, the preferred treatment in steps 1 and 2 consists of using intermittent low-dose ICS + formoterol as required. In step 3, low-dose maintenance with ICS + formoterol on a daily basis is the preferred choice. In step 4, medium-dose ICS + formoterol is the preferred treatment. In step 5, add-on LAMA therapy and refer the patient for assessment of clinical phenotype, considering high-dose maintenance ICS + LABA with/without anti-IgE, anti-IL4R, anti-IL-5, and anti-TLSP (tezepelumab).[1] Low-dose oral corticosteroid may be considered in patients with difficult access to biologics, and so are macrolides for patients with T2-low phenotypes.

When considering withdrawal of treatment or stepping down, it is advisable to do that when both asthma symptoms and lung function have remained stable for at least three months.[1] Furthermore, education of patients is one of the cornerstones of asthma treatment, involving correct use of inhaled medications, adherence to treatment, recognition of alarm signs, and lifestyle modifications. It is essential to provide training on the inhalation technique to the patient and their family members, and the technique should be reviewed at all medical appointments.[3]

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AUTHOR CONTRIBUTIONS

LHF, LG, MPP, and MAC contributed to literature review and drafting of the manuscript. PMP and LAP contributed to drafting, reviewing, and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared

REFERENCES

1. Global Initiative for Asthma (GINA) [homepage on the Internet]. Bethesda: GINA; c2023 [cited 2024 Feb 01]. 2023 GINA Report Global Strategy for Asthma Management and Prevention. Available from: https://ginasthma.org/2023-gina-main-report/
2. Levy ML, Fletcher M, Price DB, Hausen T, Halbert RJ, Yawn BP. International Primary Care Respiratory Group (IPCRG) Guidelines: diagnosis of respiratory diseases in primary care. Prim Care Respir J. 2006;15(1):20-34. https://doi.org/10.1016/j.pcrj.2005.10.004
3. Martin J, Townshend J, Brodlie M. Diagnosis and management of asthma in children. BMJ Paediatr Open. 2022;6(1):e001277. https://doi.org/10.1136/bmjpo-2021-001277
4. National Institute for Health and Care Excellence [homepage on the Internet]. London: the Institute; c2023 [cited 2024 Feb 01]. Asthma: diagnosis, monitoring and chronic asthma management (2023 update).
5. Ullmann N, Mirra V, Di Marco A, Pavone M, Porcaro F, Negro V, et al. Asthma: Differential Diagnosis and Comorbidities. Front Pediatr. 2018;6:276. https://doi.org/10.3389/fped.2018.00276
6. Zar HJ, Ferkol TW. The global burden of respiratory disease-impact on child health. Pediatr Pulmonol. 2014;49(5):430-434. https://doi.org/10.1002/ppul.23030
7. Carvalho-Pinto RM, Cançado JED, Pizzichini MMM, Fiterman J, Rubin AS, Cerci Neto A, et al. 2021 Brazilian Thoracic Association recommendations for the management of severe asthma. J Bras Pneumol. 2021;47(6):e20210273. https://doi.org/10.36416/1806-3756/e202102732021

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Overprescription of short-acting β_2 agonists: reflections from the SABINA study in Brazil

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The SABA use IN Asthma (SABINA) study in Brazil was conducted at five sites in different regions of the country: the northeastern, central-western, and southeastern regions.

ABSTRACT

Objective: To assess prescription patterns for short-acting β_2 agonists (SABAs) and other asthma medications in asthma patients treated by specialists and participating in the *SABA use IN Asthma (SABINA) study* in Brazil. **Methods:** This was an observational, cross-sectional study conducted at five sites in different regions of Brazil. The primary endpoints were to record SABA prescriptions and obtain data on over-the-counter (OTC) SABA purchases at the pharmacy. **Results:** Data on 218 asthma patients were analyzed. Of those 218 patients, 80.3% were prescribed SABAs in addition to their maintenance therapy, with a mean of 11.2 SABA canisters in the previous 12 months. Of those patients, 71.4% were prescribed ≥ 3 canisters and 42.2% were prescribed ≥ 10 canisters. None of the patients were prescribed SABA monotherapy. A total of 14.2% of the patients reported purchasing SABAs OTC at a pharmacy without a prescription. Of those, 48.4% purchased ≥ 3 SABA canisters. A fixed-dose combination of an inhaled corticosteroid and a long-acting β_2 agonist was prescribed to 95.0% of the patients. In the year before the study visit, 45.0% of the patients received at least one course of oral corticosteroid burst treatment. Asthma was well controlled in 43.1% of the patients, partly controlled in 34.9%, and uncontrolled in 22.0%. Patients reported a mean of 1.1 severe asthma exacerbations, with 49.1% experiencing 1 or more severe exacerbations. **Conclusions:** Overprescription and OTC purchases of SABAs are common in Brazil, possibly leading to the need for courses of oral corticosteroids. The health care community should collaborate to implement evidence-based recommendations and promote health education to improve asthma management in Brazil.

Keywords: Asthma; Brazil; Bronchodilator agents; Prescriptions.

INTRODUCTION

In Brazil, there are approximately 20 million patients with asthma.[1] In a study assessing data from the National Adolescent School-based Health Survey, conducted in 2012 in Brazil, it was reported that 23.2% of adolescents had asthma symptoms, and 12.4% had a previous asthma diagnosis.[2] Despite improvements in asthma diagnosis and management, the development of new therapeutic agents and targets, and updated international asthma guidelines, a large proportion of patients in Brazil remain poorly controlled.[3] Indeed, mortality rates from asthma are increasing, with data from a national database reporting that 2,488 patients died from asthma in Brazil in 2021, which equated to 7 deaths per day; moreover, there were over 120,000 hospital admissions for asthma during that year.[4]

Since 2019, following the most significant change in asthma management in three decades,[5,6] the GINA has no longer recommended the use of short-acting β_2 agonists (SABAs) without concomitant inhaled corticosteroids (ICS) for asthma patients ≥ 12 years of age.[7] Instead, on the basis of clinical evidence from randomized controlled clinical trials[8,9] and real-world studies,[10,11] the GINA now recommends a combination of low-dose ICS and the long-acting β_2 agonist (LABA) formoterol taken as needed for symptom relief for adults and adolescents with mild asthma and for those with moderate-to-severe asthma who are prescribed ICS-formoterol maintenance therapy.[7] In addition, in 2020, the Brazilian Thoracic Association (BTA) also recommended against SABA monotherapy for the treatment of asthma on the grounds of safety.[12] This decision was based on accumulating evidence that SABA monotherapy increases the risk of poorly controlled disease and severe asthma exacerbations, with the addition of ICS reducing this risk.[8,13]

There is currently limited data available on the specific patterns of and trends in asthma medication prescriptions. In particular, there is limited data on the prevalence of SABA overuse (defined as ≥ 3 canisters/year) in asthma management across Latin America. Thus, the SABA use IN Asthma (SABINA) program was developed to determine the magnitude of SABA use globally and its impact on clinical asthma outcomes

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through a real-world data analysis of harmonized large-scale observational studies. As part of this program, SABINA III, a multicenter, observational, cross-sectional study was conducted in 8,351 patients from 24 countries across five continents to describe prescription patterns of oral asthma therapies, with a particular focus on SABA prescriptions, as well as to provide an assessment of over-the-counter (OTC) SABA purchase.[14-16] This study reports results from a subanalysis of patients who participated in the SABINA III study in Brazil[14] and who were treated by different specialists, with the objective of highlighting current asthma management practices in Brazil.

METHODS

A full overview of the SABINA III methods has been published elsewhere.[14] In brief, SABINA Brazil was an observational, cross-sectional study conducted at five sites in different regions of the country (the northeastern, central-western, and southeastern regions) in private and public facilities. All patients were assessed by specialists. Recruitment occurred from March of 2019 to January of 2020. Here, we report country-specific aggregated data. The primary endpoints were to record SABA prescriptions in the 12 months preceding the study visit and obtain data on OTC SABA purchases without a prescription at the pharmacy. Prespecified patient data on asthma exacerbation history and comorbidities, as well as information on prescribed asthma medications, were collected from existing medical records by health care providers (HCPs) and collated and entered into an electronic case report form (eCRF) during a single study visit at each site. In addition, at the study visit, asthma symptom control was evaluated, and data on OTC purchases of SABAs based on patient recall were obtained directly from patients and entered in the eCRF by the investigator.

At each site, patients ≥ 12 years of age meeting the following criteria were eligible for enrollment: (i) documented physician diagnosis of asthma in their medical records; (ii) ≥ 3 previous consultations with the same HCP or practice; and (iii) medical records containing data for ≥ 12 months before the study visit. Patients with other chronic respiratory diseases, such as COPD, or an acute respiratory condition were excluded.

SABA prescriptions in the 12 months before the study visit were categorized as 0, 1-2, 3-5, 6-9, 10-12, and ≥ 13 canisters, with overprescription being defined as prescription of ≥ 3 SABA canisters/year.[14-18] Prescriptions of ICS in the previous 12 months were categorized in accordance with the prescribed average daily dose (low, medium, or high).[19] Other variables included sociodemographic characteristics, investigator-classified asthma severity (based on clinical assessment and guided by GINA 2017 treatment steps: 1-2, mild asthma; and 3-5, moderate-to-severe asthma),[19] asthma duration, and prescribed asthma treatments, including SABA monotherapy; SABAs in addition to maintenance therapy; ICS; fixed-dose combinations of ICS and LABAs; oral corticosteroid (OCS) burst treatment (defined as a short course of intravenous corticosteroids or OCSs administered for 3-10 days, or a single dose of an intramuscular corticosteroid to treat an exacerbation); and long-term OCSs (defined as any OCS treatment for > 10 days) and antibiotics. Data on pharmacy purchases of SABAs OTC without a prescription were also recorded.

Assessed asthma-related health outcomes included asthma symptom control at the time of the study visit (in accordance with the 2017 GINA definition)[19] and the number of severe asthma exacerbations 12 months before the study visit; severe asthma exacerbation was defined as a worsening of asthma symptoms resulting in hospitalization, an emergency room visit, or the need for OCS burst treatment, in accordance with the American Thoracic Society/European Respiratory Society recommendations.[20]

This study was conducted in compliance with the study protocol, the Declaration of Helsinki, and local research ethics committee approvals (CAAE no. 15624819.0.1001.5599). Written informed consent was obtained from all patients or legal guardians.

Descriptive statistics were used in order to characterize patients on the basis of their baseline demographics and clinical characteristics. Continuous variables were summarized as the number of nonmissing values, mean ± standard deviation, and median [interquartile range]. Categorical variables were summarized as frequency counts and percentages.

RESULTS

A total of 220 patients were recruited, with 219 being enrolled in the study. However, 1 patient was excluded because of the duration of asthma (i.e., < 12 months). From the five participating sites, 55.0% of the patients were recruited from the city of São Paulo or from the city of Sorocaba, both of which are located in the state of São Paulo, in southeastern Brazil; 25% were recruited from the city of Volta Redonda, located in the state of Rio de Janeiro, also in southeastern Brazil; 14.5% were recruited from the city of Salvador, located in the state of Bahia, in northeastern Brazil; and 5.5% were recruited from the city of Goiânia, located in the state of Goiás, in central-western Brazil. All participating patients were under specialist care, with 63.3% receiving treatment from pulmonologists and 36.7% receiving treatment from allergists.

Patients had a mean age of 49.0 ± 17.1 years, with the majority being female (70.6%) and never smokers (82.5%). A total of 69.3% of the patients had a BMI ≥ 25 kg/m^2, with 33.5% being classified as overweight and 35.8% being classified as obese. A total of 68.3% of the patients had a high school degree or an undergraduate/graduate degree. A little over half of the patients (51.8%) reported fully

reimbursed health care for medications and visits (Table 1).

Overall, 95.0% of the patients were classified as having moderate-to-severe asthma (GINA treatment steps 3-5) and 5.0% were classified as having mild asthma (GINA treatment steps 1-2). In this study, 41.7% of the patients were receiving GINA step 4 treatment and 37.2% were receiving GINA step 5 treatment. The mean duration of asthma was 23.2 ± 18.7 years. Patients reported a mean of 1.1 ± 1.9 severe exacerbations in the year before the study, with 49.1% experiencing 1 or more severe exacerbations. Notably, 13.5% of the patients with moderate-to-severe asthma had ≥ 3 severe exacerbations in the previous 12 months. Asthma symptom control was considered well controlled in 43.1%, partly controlled in 34.9%, and uncontrolled in 22.0%. A total of 39.0% of the patients had 1-2 comorbidities, with 45.9% reporting ≥ 3 comorbidities (Table 2).

A total of 80.3% of the patients were prescribed SABAs in addition to their maintenance therapy for symptom relief, with a mean of 11.2 ± 12.2 SABA canisters. Of those patients, 71.4% were prescribed ≥ 3 SABA canisters and 42.3% were prescribed ≥ 10 SABA canisters in the previous 12 months (Figure 1A). No prescriptions for SABA monotherapy were recorded.

A total of 14.2% of the patients reported purchasing SABAs OTC at a pharmacy without a prescription. Of those, 48.4% purchased ≥ 3 SABA canisters in the previous 12 months (Figure 1B).

A total of 34.4% of the patients received a prescription for monotherapy with ICS, with a mean of 10.5 ± 8.4 canisters prescribed in the previous 12 months. Most of the patients were prescribed high- or medium-dose ICS (49.3% and 42.7%, respectively), with only 8.0% being prescribed low-dose ICS (Table 3).

A fixed-dose combination of an ICS and a LABA was prescribed to nearly all of the patients (95.0%). Most (45.9%) received a prescription for medium-dose ICS, with 33.8% being prescribed high-dose ICS and 20.3% being prescribed low-dose ICS (Figure 1C; Table 3).

In the year before the study visit, at least one course of OCS burst treatment was prescribed to 45.0% of patients. Overall, 24.2% of the patients, most of whom had moderate-to-severe asthma, were prescribed antibiotics for their asthma.

DISCUSSION

SABINA Brazil was the first study to analyze SABA prescribing practices and OTC SABA purchases in a sample of asthma patients in different regions of Brazil;

Table 1. Demographic characteristics of the patients participating in the SABA use IN Asthma (SABINA) study in Brazil, by asthma severity.

Characteristic		Investigator-classified asthma severity		
		Mild asthma (n = 11)	Moderate-to-severe asthma (n = 207)	All patients (N = 218)
Age, years	12-17	33.9 ± 15.1	49.8 ± 16.8	49.0 ± 17.1
	≥ 18-54	35.0 [15.0-59.0]	51.0 [12.0-91.0]	51.0 [12.0-91.0]
Age group, n (%)	≥ 55	1 (9.1)	4 (1.9)	5 (2.3)
	Female	8 (72.7)	112 (54.1)	120 (55.0)
	Male	2 (18.2)	91 (44.0)	93 (42.7)
Sex, n (%)	Mean ± SD	4 (36.4)	150 (72.5)	154 (70.6)
	Median [IQR]	7 (63.6)	57 (27.5)	64 (29.4)
BMI, kg/m^2	< 18.5	32.7 ± 8.4	28.5 ± 5.7	28.7 ± 5.9
	≥ 18.5-24.9	32.9 [20.6-45.7]	27.9 [18.1-47.9]	28.1 [18.1-47.9]
BMI groups, n (%)	≥ 25-29.9	0 (0.0)	1 (0.5)	1 (0.5)
	≥ 30.0	2 (18.2)	64 (30.9)	73 (30.3)
	Elementary school	3 (27.3)	70 (33.8)	348 (33.5)
	Middle school	6 (54.5)	72 (34.8)	78 (35.8)
Educational level, n (%)	High school	1 (9.1)	39 (18.8)	40 (18.3)
	College/Graduate school	1 (9.1)	26 (12.6)	27 (12.4)
	Unknown	5 (45.5)	77 (37.2)	82 (37.6)
	Not reimbursed	4 (36.4)	63 (30.4)	67 (30.7)
	Partially reimbursed	0 (0.0)	2 (1.0)	2 (0.9)
Health insurance/medication funding, n (%)	Fully reimbursed	4 (36.4)	38 (18.4)	42 (19.3)
	Unknown	4 (36.4)	32 (15.5)	36 (16.5)
	Current smoker	1 (9.1)	112 (54.1)	113 (51.8)
	Former smoker	2 (18.2)	25 (12.1)	27 (12.4)
Smoking status, n (%)	Never smoker	1 (9.1)	4 (1.9)	5 (2.3)
	Former smoker	2 (18.2)	31 (15)	33 (15.2)
	Never smoker	8 (72.7)	171 (83)	179 (82.5)

Table 2. Characteristics of asthma in the patients participating in the SABA use IN Asthma (SABINA) study in Brazil, by asthma severity.

Characteristic		Investigator-classified asthma severity		
		Mild asthma (n = 11)	Moderate-to-severe asthma (n = 207)	All patients (N = 218)
Asthma duration, years	Mean ± SD	18.3 ± 13.8	23.4 ± 19.0	23.2 ± 18.7
	Median [IQR]	15.0 [6.0-58.0]	17.0 [1.0-85.0]	17.0 [1.0-85.0]
Number of severe asthma exacerbations in the past 12 months	Mean ± SD	1.2 ± 2.0	1.1 ± 1.8	1.1 ± 1.9
Number of severe asthma exacerbations in the past 12 months by group, n (%)	0	8 (72.7)	103 (49.8)	111 (50.9)
	1	0 (0.0)	45 (21.7)	45 (20.6
	2	0 (0.0)	31 (15.0)	31 (14.2)
	3	0 (0.0)	16 (7.7)	16 (7.3)
	> 3	3 (27.3)	12 (5.8)	15 (6.9)
GINA classification, n (%)	Step 1	1 (9.1)	0 (0.0)	1 (0.5)
	Step 2	10 (90.9)	0 (0.0)	10 (4.6)
	Step 3	0 (0)	35 (16.9)	35 (16.1)
	Step 4	0 (0)	91 (44.0)	91 (41.7)
	Step 5	0 (0)	81 (39.1)	81 (37.2)
Level of asthma symptom control, n (%)	Well controlled	4 (36.4)	90 (43.5)	94 (43.1)
	Partly controlled	5 (45.5)	71 (34.3)	76 (34.9)
	Not controlled	2 (18.2)	46 (22.2)	48 (22)
Number of comorbidities, n (%)	0	0 (0.0)	33 (15.9)	33 (15.1)
	1-2	5 (45.5)	80 (38.6)	85 (39.0)
	3-4	4 (36.4)	58 (28.0)	62 (28.4)
	≥ 5	2 (18.1)	36 (17.5)	38 (17.5)

therefore, this study provides valuable information on prescribing habits for asthma at the specialist care level in Brazil. Overall, the findings show an unmet need in terms of further education, training in asthma management, and other treatment options, such as additional therapy with biologic agents, highlighting the fact that SABA overprescription is an area of notable concern in Brazil. This topic was addressed in a position statement on SABA use in asthma management in Latin America, where overreliance on the use of SABAs is a major public health concern that needs to be addressed at all levels of health care.[21]

In contrast to what was observed in many of the participating countries in SABINA III, all (100%) of the patients in Brazil were overseen by specialists at asthma referral centers; this accounts for the finding that most (95.0%) of the patients were classified as having moderate-to-severe asthma and were prescribed fixed-dose combination therapy with ICS and LABAs, with none of the patients having been prescribed SABA monotherapy. In 2020, BTA-recommended treatment steps 4 and 5 included the prescription of SABAs as rescue therapy. Because patients were seen by specialists, SABA monotherapy prescriptions were not recorded, in accordance with the guidelines. Nevertheless, it is important to emphasize that, despite receiving specialist care, nearly a quarter of the patients (22.0%) reported uncontrolled asthma in the 12 months before the study visit. Moreover, in patients who were prescribed SABAs in addition to maintenance therapy, 71.4% and 42.3% were prescribed ≥ 3 and ≥ 10 SABA canisters, respectively, in the preceding 12 months. Factors that may have contributed to these high rates of SABA prescribing include the free provision of certain asthma medications, including albuterol, to patients with asthma by the Brazilian Unified Health Care System[22] and the high cost of combined ICS-LABA inhalers.[23] Crucially, patients also obtained SABAs through unregulated sources, with 14.2% of the patients having purchased SABAs OTC without a prescription. Of those, 48.4% purchased ≥ 3 canisters. This finding reinforces patient overreliance on SABA therapy for symptom relief and is of concern because SABA purchase further increases the potential for SABA overuse.[24] Since OTC purchase of SABAs has been linked to a decrease in medical visits, an increase in emergency room visits, and low use of prescription medications, thus contributing to suboptimal treatment of asthma,[25-27] it is essential to improve accessibility to health care, make medications more affordable, and better regulate OTC SABA purchases.

The prevalence of uncontrolled asthma was lower in SABINA Brazil than in previous studies conducted in Brazil[3] and Latin America,[28-30] indicating improved asthma outcomes from specialist care. Nevertheless, the high rate of severe asthma exacerbations and the low proportion of patients with well-controlled asthma clearly illustrate a significant opportunity to further optimize asthma management. In addition,

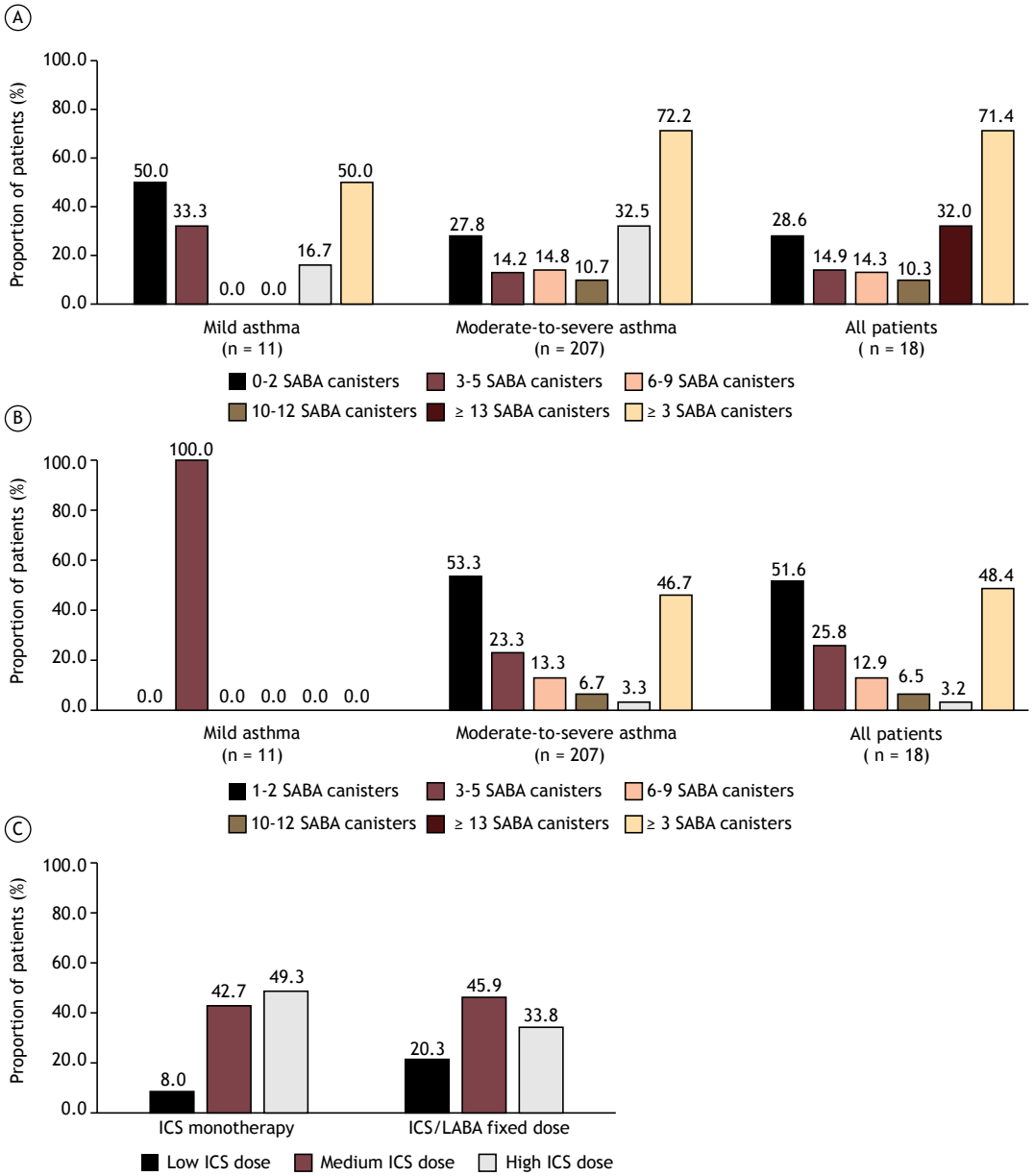

Figure 1. In A, short-acting β_2 agonist (SABA) prescriptions, by asthma severity; in B, over-the-counter (OTC) SABA purchases, by asthma severity; and in C, inhaled corticosteroid (ICS) prescriptions, by dose, in the 12 months before the study visit in the SABA use IN Asthma (SABINA) study in Brazil. LABA: long-acting β_2 agonist.

the high rates of SABA overprescription, coupled with the fact that less than 50% of the patients participating in SABINA Brazil reported well-controlled asthma, further underscore the need for strategies to overcome barriers currently limiting the attainment of asthma control across the country to decrease asthma morbidity and mortality. This is of particular importance given that increasing SABA exposure increases the risk of severe exacerbations.[14,16-18] Indeed, the SABINA I study conducted in the UK showed that the use of ≥ 3 SABA canisters per year significantly increased the risk of exacerbations and health care utilization (primary care and hospital outpatient consultations). [17] Additionally, findings from Sweden (SABINA II) showed that an increasing number of collected SABA canisters increased the risk of exacerbations, with higher SABA use being also associated with increased mortality risk.[18] Moreover, aggregated data from all 24 countries in SABINA III, as well as the Latin American cohort of SABINA III, which included 1,096 patients from Argentina, Brazil, Chile, Colombia, Costa Rica, and Mexico, indicated that, in comparison with 1-2 SABA prescriptions per year, ≥ 3 SABA prescriptions per year were associated with increasingly lower odds of controlled or partly controlled asthma and higher rates of severe exacerbations across asthma severities and primary and specialist care settings.[14,16]

Table 3. Prescription of other medications in the previous 12 months in the SABA use IN Asthma (SABINA) study in Brazil.

	Investigator-classified asthma severity		
	Mild asthma (n = 11)	Moderate-to-severe asthma (n = 207)	All patients (N = 218)
Prescription of ICS, n (%)			
No	7 (63.6)	136 (65.7)	143 (65.6)
Yes	4 (36.4)	71 (34.3)	75 (34.4)
ICS canisters or inhalers prescribed in the past 12 months			
Mean ± SD	10.0 ± 10.5	10.5 ± 8.4	10.5 ± 8.4
Median [IQR]	7.5 [1.0-24.0]	10.0 [1.0-48.0]	10.0 [1.0-48.0]
Total daily ICS dose, n (%)			
Low dose	1 (25.0)	5 (7.0)	6 (8.0)
Medium dose	2 (50.0)	30 (42.3)	32 (42.7)
High dose	1 (25.0)	36 (50.7)	37 (49.3)
Prescription of ICS/LABA fixed-dose combination, n (%)			
No	6 (54.5)	5 (2.4)	11 (5.0)
Yes	5 (45.5)	202 (97.6)	207 (95.0)
Total daily ICS dose, n (%)			
Low dose	5 (100.0)	37 (18.3)	42 (20.3)
Medium dose	0 (0.0)	95 (47.0)	95 (45.9)
High dose	0 (0.0)	70 (34.7)	70 (33.8)
Prescription of OCS burst treatment/short course, n (%)			
No	7 (63.6)	113 (54.6)	120 (55.0)
Yes	4 (36.4)	94 (45.4)	98 (45.0)
Total daily dose, mg/day			
Mean ± SD	40.0 ± 0.0	47.2 ± 68.3	46.9 ± 66.9
Median [IQR]	40.0 [40.0-40.0]	40.0 [5.0-500.0]	40.0 [5.0-500.0]
Number of days per prescription			
Mean ± SD	5.0 ± 0.0	5.5 ± 2.0	5.5 ± 2.0
Median [IQR]	5.0 [5.0-5.0]	5.0 [1.0-15.0]	5.0 [1.0-15.0]
Prescription of antibiotics for asthma, n (%)			
No	10 (90.9)	153 (73.9)	163 (75.8)
Yes	1 (9.1)	51 (24.6)	52 (24.2)

ICS: inhaled corticosteroid(s); LABA: long-acting β_2 agonist; and OCS: oral corticosteroid.

For over 50 years, as-needed SABA therapy was the preferred therapeutic approach for symptom relief. Although guidelines now endorse an ICS-containing reliever, results from several clinical studies and real-world evidence studies have documented the magnitude of SABA monotherapy.[14,16,31-35] Therefore, access to combination therapy should be prioritized, particularly because ICS-formoterol as maintenance and reliever therapy reduces exacerbation rates, thereby alleviating the burden on health care services.[36-38] These approaches should be followed by educational initiatives targeted at patients and relevant stakeholders, including physicians and pharmacists, to raise awareness and increase understanding around the latest treatment recommendations. The development of national asthma programs based on current evidence-based guidelines, which can be adapted to clinical settings and practices, together with the creation of local resources, will play an essential role in this endeavor. In addition to these measures, changes to evidence-based treatment guidelines as proposed by the GINA[6] and the BTA,[12] which now recommend ICS-formoterol as the as-needed reliever of choice for adults and adolescents across treatment steps, represent a significant step toward combating SABA overuse and reducing the risk of severe exacerbations across all severities of asthma.

Findings from this study need to be considered in the context of a number of limitations. First, although patients were recruited from different regions of Brazil, it was only possible to obtain a relatively small patient sample. Second, the number of cigarettes used by current or former smokers (in pack-years) was not collected. Third, all patients were recruited from specialist care; therefore, this population may not be representative of the entire asthma population in Brazil or provide an accurate assessment of how patients with asthma are being managed in this country. Fourth, recruitment occurred prior to the approval of biologic agents in the public health care system, and patients were under the care of a specialist in accordance with Brazilian recommendations. Fifth, it is possible that not all SABA prescriptions translated into actual use; therefore, it is entirely possible

that SABA use was actually lower. Sixth, SABA overprescription, especially in the emergency room, and the vicious cycle of OTC SABA purchase at the pharmacy, resulting in self-medication and random treatment, may have increased the potential for incorrect patient assessments. Seventh, the fact that no patients were seen by primary care physicians was a deviation from the original study design as it was specified in the protocol and may have resulted in improved prescribing practices and patient outcomes when compared with those recorded in SABINA studies in which primary care physicians participated. In addition, this precluded a comparison of results across primary and specialist care. On the other hand, the exclusion of patients managed at the primary care level in this study underscores the requirement for further education and training of general practitioners to ensure that they are able to diagnose and manage patients with complex asthma, without the need for referral centers. Finally, factors potentially contributing to SABA overuse were not investigated, and this is an area that requires further research and assessment. Despite these limitations, this study provides real-world data on SABA prescription patterns and OTC SABA purchase in Brazil, highlighting that asthma continues to exert a major social and economic burden across the country and reinforcing the need to adhere to the latest treatment guidelines to improve treatment outcomes for patients with asthma in Brazil.

In conclusion, the results of SABINA Brazil show SABA overprescription (≥ 3 canisters/year) in nearly three quarters of all patients (71%), with 42% receiving prescriptions for ≥ 10 SABA canisters. Moreover, SABA overprescription was associated with poor asthma control and an increased risk of severe asthma exacerbations, placing patients at an increased risk of adverse events and even mortality. In addition, SABA overprescription and OTC SABA purchase were common in this analysis, possibly leading to the need for courses of OCSs. The health care community should collaborate to implement evidence-based recommendations and promote health education to improve asthma management.

DATA AVAILABILITY

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

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AUTHOR CONTRIBUTIONS

MJHIB designed the study. All authors contributed to data analysis, data interpretation, and drafting and reviewing of the manuscript.

CONFLICTS OF INTEREST

MAA participated in clinical trials for AbbVie, AstraZeneca, EMS, Eurofarma, GlaxoSmithKline, Humanigen, Janssen, Novartis, Sanofi, and Veru, and received fees for conferences and consultancy activities from Abbott, Aché, AstraZeneca, Chiesi, Eurofarma, IPI ASAC, and Sanofi. ASM gives lectures and develops clinical trials for AstraZeneca and Sanofi; has a project funded by the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development); and is an associate professor 4 at the Federal University of Bahia Institute of Health Sciences, located in the city of Salvador, Brazil. MGG develops clinical trials for AstraZeneca. AAC is a professor of medicine at the Federal University of Bahia and the executive director of the ProAR Foundation. He received honoraria for lectures and/or advisory boards from Abdi Ibrahim, AstraZeneca, Boehringer Ingelheim, Chiesi, Crossject, Eurofarma, Glenmark, GlaxoSmithKline, Mylan, Novartis, and Sanofi. LA is an employee of AstraZeneca. MJHIB was an employee of AstraZeneca at the time the study was conducted. GAZ develops clinical trials for AstraZeneca and is an assistant professor of medicine at the *Centro Universitário de Volta Redonda*, Brazil. MFR was principal investigator of clinical studies for AstraZeneca, Boehringer Ingelheim, and Eurofarma.

REFERENCES

1. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma - 2012. J Bras Pneumol. 2012;38(Suppl 1):S1-S46.
2. Barreto ML, Ribeiro-Silva Rde C, Malta DC, Oliveira-Campos M, Andreazzi MA, Cruz AA. Prevalence of asthma symptoms among adolescents in Brazil: National Adolescent School-based Health

Survey (PeNSE 2012). Rev Bras Epidemiol. 2014;17 Suppl 1:106-115. https://doi.org/10.1590/1809-4503201400050009

3. Cançado JED, Penha M, Gupta S, Li VW, Julian GS, Moreira ES. Respira project: Humanistic and economic burden of asthma in Brazil. J Asthma. 2019;56(3):244-251. https://doi.org/10.1080/02770903.2018.1445267
4. Brasil, Ministério da Saúde. Plataforma integrada de vigilância em saúde [homepage on the Internet]. Brasília: o Ministério; c2023 [cited 2023 Sep 26]. Painel de Monitoramento da Mortalidade CID-10. Available from: http://plataforma.saude.gov.br/mortalidade/cid10/
5. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019;53(6):1901046. https://doi.org/10.1183/13993003.01046-2019
6. Global Initiative for Asthma [homepage on the Internet]. Bethesda: Global Initiative for Asthma; c2019 [cited 2023 Jan 25]. Global Strategy for Asthma Management and Prevention (2019 update). Available from: https://ginasthma.org/gina-reports/
7. Global Initiative for Asthma (GINA) [homepage on the Internet]. Bethesda: GINA; c2022 [cited 2023 Jan 25]. Global Strategy for Asthma Management and Prevention (Updated 2022). Available from: https://ginasthma.org/gina-reports/
8. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018;378(20):1865-1876. https://doi.org/10.1056/nejmoa1715274
9. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med. 2018;378(20):1877-1887. https://doi.org/10.1056/nejmoa1715275
10. Cheng SL, Ho ML, Lai YF, Wang HC, Hsu JY, Liu SF, et al. Budesonide/Formoterol Anti-Inflammatory Reliever and Maintenance or Fluticasone Propionate/Salmeterol Plus As-Needed, Short-Acting β_2 Agonist: Real-World Effectiveness in pAtients without Optimally Controlled asThma (REACT) Study [published correction appears in Drug Des Devel Ther. 2021 Feb 12;15:515-516]. Drug Des Devel Ther. 2020;14:5441-5450. https://doi.org/10.2147/DDDT.S266177
11. Zhong N, Lin J, Mehta P, Ngamjanyaporn P, Wu TC, Yunus F. Real-life effectiveness of budesonide/formoterol maintenance and reliever therapy in asthma patients across Asia: SMARTASIA study. BMC Pulm Med. 2013;13:22. https://doi.org/10.1186/1471-2466-13-22
12. Pizzichini MMM, Carvalho-Pinto RM, Cançado JED, Rubin AS, Cerci Neto A, Cardoso AP, et al. 2020 Brazilian Thoracic Association recommendations for the management of asthma. J Bras Pneumol. 2020;46(1):e20190307. https://doi.org/10.1590/1806-3713/e20190307
13. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med. 1991;325(6):388-392. https://doi.org/10.1056/nejm199108083250603
14. Short-acting β_2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. Eur Respir J. 2022;59(5):2101402. https://doi.org/10.1183/13993003.01402-2021
15. Cabrera CS, Nan C, Lindarck N, Beekman MJHI, Arnetorp S, van der Valk RJP. SABINA: global programme to evaluate prescriptions and clinical outcomes related to short-acting β_2-agonist use in asthma. Eur Respir J. 2020;55(2):1901858. https://doi.org/10.1183/13993003.01858-2019
16. Montero-Arias F, Garcia JCH, Gallego MP, Antila MA, Schonffeldt P, Mattarucco WJ, et al. Over-prescription of short-acting β_2-agonists is associated with poor asthma outcomes: results from the Latin American cohort of the SABINA III study. J Asthma. 2023;60(3):574-587. https://doi.org/10.1080/02770903.2022.2082305
17. Bloom CI, Cabrera C, Arnetorp S, Coulton K, Nan C, van der Valk RJP, et al. Asthma-Related Health Outcomes Associated with Short-Acting β_2-Agonist Inhaler Use: An Observational UK Study as Part of the SABINA Global Program. Adv Ther. 2020;37(10):4190-4208. https://doi.org/10.1007/s12325-020-01444-5
18. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020;55(4):1901872. https://doi.org/10.1183/13993003.01872-2019
19. Global Initiative for Asthma (GINA) homepage on the Internet]. Bethesda: GINA [cited 2023 Jan 25]. Global Strategy for Asthma Management and Prevention, 2017. Available from: https://ginasthma.org/gina-reports/
20. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59-99. https://doi.org/10.1164/rccm.200801-060st
21. Nannini LJ, Luhning S, Rojas RA, Antunez JM, Miguel Reyes JL, Cano Salas C, et al. Position statement: asthma in Latin America. IS short-acting beta-2 agonist helping or compromising asthma management?. J Asthma. 2021;58(8):991-994. https://doi.org/10.1080/02770903.2020.1777563
22. Comaru T, Pitrez PM, Friedrich FO, Silveira VD, Pinto LA. Free asthma medications reduces hospital admissions in Brazil (Free asthma drugs reduces hospitalizations in Brazil). Respir Med. 2016;121:21-25. https://doi.org/10.1016/j.rmed.2016.10.008
23. The Global Asthma Network (GAN) [homepage on the Internet]. c2023; [cited 2023 Jan 25]. The Global Asthma Report 2018. Available from: http://globalasthmareport.org/2018/index.html
24. Blakeston S, Harper G, Zabala Mancebo J. Identifying the drivers of patients' reliance on short-acting β2-agonists in asthma. J Asthma. 2021;58(8):1094-1101. https://doi.org/10.1080/02770903.2020.1761382
25. Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. BMJ Open. 2017;7(9):e016688. https://doi.org/10.1136/bmjopen-2017-016688
26. Gibson P, Henry D, Francis L, Cruickshank D, Dupen F, Higginbotham N, et al. Association between availability of non-prescription beta 2 agonist inhalers and undertreatment of asthma. BMJ. 1993;306(6891):1514-1518. https://doi.org/10.1136/bmj.306.6891.1514
27. Henry DA, Sutherland D, Francis L. The use of non-prescription salbutamol inhalers by asthmatic patients in the Hunter Valley, New South Wales. Newcastle Retail Pharmacy Research Group. Med J Aust. 1989;150(8):445-449. https://doi.org/10.5694/j.1326-5377.1989.tb136566.x
28. Maspero JF, Jardim JR, Aranda A, Tassinari CP, Gonzalez-Diaz SN, Sansores RH, et al. Insights, attitudes, and perceptions about asthma and its treatment: findings from a multinational survey of patients from Latin America. World Allergy Organ J. 2013;6(1):19. https://doi.org/10.1186/1939-4551-6-19
29. Alith MB, Gazzotti MR, Nascimento OA, Jardim JR. Impact of asthma control on different age groups in five Latin American countries. World Allergy Organ J. 2020;13(4):100113. https://doi.org/10.1016/j.waojou.2020.100113
30. Neffen H, Moraes F, Viana K, Di Boscio V, Levy G, Vieira C, et al. Asthma severity in four countries of Latin America. BMC Pulm Med. 2019;19(1):123. https://doi.org/10.1186/s12890-019-0871-1
31. Alzaabi A, Al Busaidi N, Pradhan R, Shandy F, Ibrahim N, Ashtar M, et al. Over-prescription of short-acting β_2-agonists and asthma management in the Gulf region: a multicountry observational study. Asthma Res Pract. 2022;8(1):3. https://doi.org/10.1186/s40733-022-00085-5
32. Khattab A, Madkour A, Ambaram A, Smith C, Muhwa CJ, Mecha JO, et al. Over-prescription of short-acting β_2-agonists is associated with poor asthma outcomes: results from the African cohort of the SABINA III study. Curr Med Res Opin. 2022;38(11):1983-1995. https://doi.org/10.1080/03007995.2022.2100649
33. Al Zaabi A, Busaidi N, Al Mutairy S, Yorgancıoğlu A, Aksu K, Al-Jahdali H, et al. Overprescription of short-acting β_2-agonists is associated with poor asthma symptom control: results from five Middle Eastern countries included in the SABINA International (III) study. Expert Rev Respir Med. 2022;16(7):833-847. https://doi.org/10.1080/17476348.2022.2099841
34. FitzGerald JM, Tavakoli H, Lynd LD, Al Efraij K, Sadatsafavi M. The impact of inappropriate use of short acting beta agonists in asthma. Respir Med. 2017;131:135-140. https://doi.org/10.1016/j.rmed.2017.08.014

35. Azzi EA, Kritikos V, Peters MJ, Price DB, Srour P, Cvetkovski B, et al. Understanding reliever overuse in patients purchasing over-the-counter short-acting beta$_2$ agonists: an Australian community pharmacy-based survey. BMJ Open. 2019;9(8):e028995. https://doi.org/10.1136/bmjopen-2019-028995

36. Ställberg B, Ekström T, Neij F, Olsson P, Skoogh BE, Wennergren G, et al. A real-life cost-effectiveness evaluation of budesonide/formoterol maintenance and reliever therapy in asthma. Respir Med. 2008;102(10):1360-1370. https://doi.org/10.1016/j.rmed.2008.06.017

37. Jenkins CR, Bateman ED, Sears MR, O'Byrne PM. What have we learnt about asthma control from trials of budesonide/formoterol as maintenance and reliever? [published correction appears in Respirology. 2020 Oct;25(10):1103-1104]. Respirology. 2020;25(8):804-815. https://doi.org/10.1111/resp.13804

38. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martínez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007;61(5):725-736. https://doi.org/10.1111/j.1742-1241.2007.01338.x

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ORIGINAL ARTICLE

Clinical outcomes before and after videofluoroscopic swallow study in children 24 months of age or younger

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ABSTRACT

Objective: To evaluate the combined impact of videofluoroscopic swallow study (VFSS) and therapeutic feeding and swallowing interventions on clinical outcomes in children with oropharyngeal dysphagia (OPD). **Methods:** This was an uncontrolled longitudinal analytical study in which OPD patients were evaluated before and after VFSS. Children ≤ 24 months of age diagnosed with OPD in a clinical setting and undergoing VFSS for investigation and management of OPD were included in the study. The study participants received therapeutic feeding and swallowing interventions after having undergone VFSS, being followed at an outpatient clinic for pediatric dysphagia in order to monitor feeding and swallowing difficulties. Respiratory and feeding outcomes were compared before and after VFSS. **Results:** Penetration/aspiration events were observed in 61% of the VFSSs (n = 72), and therapeutic feeding and swallowing interventions were recommended for 97% of the study participants. After the VFSS, there was a reduction in the odds of receiving antibiotic therapy (OR = 0.007) and in the duration of antibiotic therapy (p = 0.014), as well as in the odds of being admitted to hospital (p = 0.024) and in the length of hospital stay (p = 0.025). A combination of oral and enteral feeding became more common than oral or enteral feeding alone (p = 0.002). **Conclusions:** A high proportion of participants exhibited penetration/aspiration on VFSS. Therapeutic feeding and swallowing interventions following a VFSS appear to be associated with reduced respiratory morbidity in this population.

Keywords: Fluoroscopy; Deglutition disorders; Respiratory tract diseases; Pneumonia, aspiration; Nutritional support.

INTRODUCTION

Swallowing and feeding require active coordination of the oropharyngeal mechanism, craniofacial structures, gastrointestinal tract, cardiopulmonary system, musculoskeletal system, central nervous system, and peripheral nervous system.[1] Oropharyngeal dysphagia (OPD) refers to impaired oral, pharyngeal, or oropharyngeal swallowing mechanics.[2]

The rate of diagnosis of OPD has increased as a result of improved diagnostic techniques and treatment in children with complex health conditions.[2-4] OPD is related to an increased risk of (acute or recurrent) aspiration of secretions, liquids, or food particulates,[5] representing a serious cause of morbidity and mortality in children (and a cause of morbidity in caregivers).[1,6-8] Some children with OPD continue to have lower respiratory tract infections and other respiratory diseases even after treatment. Patients presenting with recurrent lower respiratory tract infections without other overt signs of swallowing dysfunction should undergo a workup for dysphagia.[7,9]

Impaired swallowing biomechanics, as assessed by videofluoroscopic swallow study (VFSS), has been associated with increased respiratory morbidity.[9-15] OPD should be considered in any child presenting with unspecified respiratory difficulties.[7] Little is known about the predictive value of VFSS or the extent to which VFSS can contribute to the management of OPD, especially with regard to respiratory, nutritional, and developmental factors.[13,14] Thus, the objective of the present study was to evaluate the combined impact of VFSS and therapeutic feeding and swallowing interventions on clinical outcomes in children with OPD.

METHODS

This was an uncontrolled longitudinal analytical study conducted at the *Hospital de Clínicas de Porto Alegre*,

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a tertiary hospital located in the city of Porto Alegre, Brazil. The study was approved by the local research ethics committee (Protocol no. 2015.0418). The study sample consisted of patients followed at the *Hospital de Clínicas de Porto Alegre* Outpatient Clinic for Pediatric Dysphagia. All of the patients had been referred to the clinic by specialists at our hospital. The clinic provides dysphagia patients and their families/primary caregivers by guiding them on safe and efficient feeding approach during visits occurring monthly or more frequently as needed.

The inclusion criteria were as follows: being ≤ 24 months of age; having chronic respiratory symptoms; having undergone a clinical assessment of swallowing by a speech therapist; and having subsequently undergone a VFSS for assessment and management of OPD, in accordance with the American Speech-Language-Hearing Association guidelines.[16] Children were excluded if their electronic medical records contained no information regarding the VFSS or if < six months had passed since the VFSS.

The outcomes of interest were compared between two six-month periods (before and after the VFSS). For children < 6 months of age, the analysis period prior to the VFSS corresponded to their age. The following outcomes were evaluated: feeding route; hospitalization; and antibiotic therapy for respiratory infections. After analysis of the VFSS results, the primary caregivers were given guidance on the treatment of OPD, in accordance with the American Speech-Language-Hearing Association recommendations,[17] and the patients were followed at the *Hospital de Clínicas de Porto Alegre* Outpatient Clinic for Pediatric Dysphagia. The data were retrospectively collected from patient medical records.

The therapeutic interventions consisted of changes in food consistency, changes in feeding posture, changes in patient positioning, and use of utensils tailored to patient needs.[17] During the VFSS, efforts were made to maintain well-established home practices, although modifications aimed at increasing swallowing safety were made when necessary.

All VFSSs were performed with continuous fluoroscopy (Axiom Iconos R100 fluoroscopy system; Siemens Healthineers, Erlangen, Germany), with a maximum total duration of 150 s, a standard resolution of 30 frames per second, and radiation exposure as low as reasonably achievable, obtaining relevant information in the minimum possible time.[18] Images were recorded in digital format in a picture archiving and communication system for subsequent analysis. Barium sulfate was used as contrast at a concentration of 30%. Results were stored digitally. The VFSS was performed and analyzed by a speech-language pathologist and a radiologist with at least 20 years of experience in pediatric OPD and radiographic swallow studies.

All VFSS images were obtained with the patient in a lateral position. The primary caregiver was given the opportunity to accompany the patient, wearing the required protective equipment. The outcome variables for this study were the presence or absence of isolated penetration and the presence or absence of aspiration. The most severe finding among all consistencies tested was reported. For patients with previous or current evidence of aspiration, not all food consistencies were tested, given that aspiration was a concern.

Patient characterization included neonatal data. For those born prematurely, the age was corrected on the basis of gestational age at birth for analysis. Comorbidities such as central nervous system impairment, respiratory disease, and genetic disease were categorized.

Respiratory outcomes included duration of antibiotic therapy (in days), number of hospitalizations, and length of stay (in days) associated with pneumonia, asthma, bronchiolitis, bronchitis, acute respiratory failure, and other upper and lower airway infections. Respiratory diseases were analyzed as a single variable because of the diagnostic complexity of signs and symptoms in patients with OPD[6,7] and their relationship with manifestations of respiratory disease.[7,9,10,12,14,15]

Feeding routes were classified as follows: exclusively oral feeding; a combination of oral and enteral feeding; or exclusively enteral feeding. Therapeutic feeding and swallowing interventions after VFSS were classified as follows: no modifications; maintenance or initiation of oral feeding; discontinuation or continued suspension of oral feeding (contraindication of oral feeding and mandatory referral for speech-language therapy); or maintenance or initiation of a combination of oral and enteral feeding.

The Kolmogorov-Smirnov test was used in order to test the normality of the distribution. Variables were described as median [interquartile range] for continuous variables and as absolute and relative frequencies for categorical variables. Categorical variables were analyzed with Fisher's exact test or Pearson's chi-square test.

For paired groups, McNemar's test and the Wilcoxon test were used. Unpaired groups were compared by the Mann-Whitney U test or the Kruskal-Wallis test. All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). The level of significance was set at $p < 0.05$. Multiple linear regression and generalized linear models were used in order to assess associations and correlations between clinical outcomes before and after VFSS, being adjusted for patient age at testing. Associations were expressed as ORs and 95% CIs.

RESULTS

Seventy-two children were included in the study. Of those, 43 (59.72%) underwent VFSS during

hospitalization. In addition, 21 (29.17%) had been advised to modify food consistency. The clinical characteristics of the study participants are described in Table 1.

On VFSS, most of the study participants showed penetration/aspiration. The aspiration events were silent in most cases. Although 38.9% of the study participants had a VFSS without penetration/aspiration, only 2 (2.8%) did not receive a recommendation to change their feeding strategies (Table 2).

Children who showed penetration/aspiration on VFSS were younger (median age, 4.5 months; IQR, 1-12.75 months) than were those who did not (median age, 8.5 months; IQR, 4.25-15.75 months; p = 0.039). Children born prematurely (n = 28) showed a higher frequency of penetration/aspiration (n = 20; 71.42%) than did those born at term (n = 19; 52.73%), although the difference was not significant (p = 0.129).

Table 1. Clinical characteristics of the participating patients (n = 72).[a]

Characteristic	Result
Age	6 [2.00-13.75]
< 12 months	50 (69.4)
≥ 12 months	22 (30.6)
Newborn characteristics	
Male sex	44 (61.1)
Median gestational age, weeks/days (n = 65)	37 [34]/2 [5-39]
Premature birth (n = 65)	28 (43.1)
Low birth weight (n = 45)	14 (31.1)
Length of hospital stay, days (n = 71)	37 [13.5-60.0]
Comorbidities	
Respiratory disease	49 (68.1)
Genetic disease	33 (45.8)
CNS impairment	33 (45.8)
Upper airway surgery	23 (31.9)
Cardiac impairment	25 (34.7)
Digestive impairment	18 (25)
Prematurity (n = 65)	28 (43.1)
Number of comorbidities	2 [1-2]

CNS: central nervous system. [a]Data expressed as median [IQR] or n (%).

Table 2. Results of videofluoroscopic swallow study and recommended feeding strategies (n = 72).[a]

VFSS result	Participant
Absence of penetration/aspiration	28 (38.9)
Penetration	25 (34.7)
Aspiration	19 (26.4)
Silent aspiration (n = 19)	17 (89.47)
Aspiration with cough (n = 19)	2 (10.53)
Recommended feeding strategy	
None	2 (2.8)
Oral feeding only	37 (51.4)
Initiate or maintain enteral feeding exclusively	18 (25)
Oral + enteral feeding	15 (20.8)

VFSS: videofluoroscopic swallow study. [a]Data expressed as n (%).

With regard to feeding routes, there were no significant differences between groups before and after the VFSS, being respectively 31 (43.1%) and 29 (40.3%) for oral feeding (p = 0.0842), 22 (30.6%) and 25 (34.7%) for a combination of oral and enteral feeding (p = 0.711), and 19 (26.4%) and 18 (25%) for enteral feeding (p = 1). However, with regard to changes in feeding routes during follow-up, there was a significant change in the number of patients in each group (p = 0.002).

When we compared the six-month periods before and after the VFSS, we found that there was an improvement in respiratory outcomes. The age-adjusted logistic regression model showed that the probability of being hospitalized decreased by 85% (p < 0.001) and the probability of not using antibiotics increased by 1.47 times (p = 0.007) after the VFSS and implementation of therapeutic feeding and swallowing interventions (Table 3). The multivariate model (Table 4) showed reductions in the length of hospital stay (p = 0.024) and duration of antibiotic therapy (p = 0.014). The number of hospitalizations (p = 0.037) did not remain significant after adjustment for age (p = 0.072).

DISCUSSION

The present study analyzed clinical outcomes before and after VFSS in a group of children referred to an outpatient clinic for pediatric dysphagia. In the period following the VFSS and therapeutic feeding and swallowing interventions, the probability of being hospitalized and using antibiotics was lower, as were the length of hospital stay and duration of antibiotic therapy for respiratory infections. The statistical models adjusted for age confirmed the results and the strength of the associations, the exception being the number of hospitalizations. We believe that although the number of hospital admissions did not change, the severity of these admissions was greater before the VFSS, as evidenced by other indicators of respiratory morbidity.

Benfer et al.[19] reported that, in children, the odds of having OPD decrease with increasing age and increase with increasing Gross Motor Function Classification System (GMFCS) level. However, they found that the reduction in OPD was significant only for children with GMFCS levels I and II. Although with time and conservative management many infants with aspiration will improve (within 1-2 years),[14,20] the authors reported that there was a lack of detailed intervention data and that they were unable to determine whether the changes were related to the provision of feeding interventions or were reflective of the early natural history of cerebral palsy (which for the sample had a mean of 27.3 months).[19] In contrast, our study evaluated clinical outcomes

before and after interventions (VFSS and specialized management of OPD) for a maximum period of 12 months, controlling for age.

During follow-up, the prevalence of a combination of oral and enteral feeding increased in comparison with that of oral or enteral feeding alone, highlighting the importance of tailored treatment.

The predominance of children < 12 months of age at the time of the VFSS in the present study, as well as the association between penetration/aspiration in younger children, can be explained by the process of physiological maturation. Safe swallowing requires active coordination of the central and peripheral nervous systems, the cardiopulmonary system, and the gastrointestinal tract, all of which develop through childhood.[1,21] In addition to the process of maturation, fewer changes on VFSS in older children might reflect the adoption of better feeding practices by caregivers, either spontaneously or under professional supervision.

We found a high prevalence of penetration/aspiration on VFSS in the study population. Penetration/aspiration is the most common finding of swallowing impairment in the literature. Although we agree that it is important to expand and describe quantitative swallowing measures to assist in clinical decision-making,[22,23] the objective of this study was to evaluate patient clinical course, the VFSS results being used as complementary data. Because of the risk of radiation exposure, VFSS referrals should be carefully considered, ideally in conjunction with clinical evaluation of swallowing by an experienced professional, who can identify signs suggestive of aspiration.[2,7,16,20] The absence of mechanisms of airway protection from aspiration (silent aspiration) was prevalent in the present study, corroborating previous findings in the pediatric population,[2,22,24,25] especially in children < 24 months of age in whom protective vagal reflexes are not fully developed.[2]

Therapeutic feeding and swallowing interventions following the VFSS in most of the children in the present study, including those with less evident signs and symptoms of DOF such as penetration/aspiration, are justified because of the primary objective of the VFSS, which is to assess feeding safety and the effectiveness of compensatory feeding strategies.[2,7,16,22,23] During the follow-up period, feeding strategies were modified despite the absence of severe findings on the VFSS. Therefore, we believe that VFSS findings alone do not provide appropriate evaluation and management of children with OPD.[10] The diagnosis and treatment of OPD should be based on clinical impression (clinical evaluation and history of episodes of aspiration pneumonia) and objective findings of changes in swallowing biomechanics.[26]

In the present study, VFSS findings of OPD followed by therapeutic management were associated with reduced respiratory morbidity. This suggests that airway protection can be achieved with greater attention to OPD. We found two studies evaluating outcomes before and after interventions in children with neurodevelopmental impairment. Silverio & Henrique[27] reported a decrease in respiratory events after speech and language therapy; however, their findings were based only on clinical diagnostic protocols for OPD. Sullivan et al.[28] performed VFSS on some of their patients and observed a decrease in the number of lung infections after gastrostomy.

Many of the children in the current study had a combination of oral and enteral feeding introduced during the follow-up period. This means that oral feeding was initiated in patients who had previously received enteral feeding alone and that there was an increase in the number of children who originally received oral feeding and who were started on a combination of oral and enteral feeding. These findings suggest that the recommendation of complementary feeding strategies was based on nutritional factors as well, rather than on OPD alone. Previous studies have hypothesized or showed that there is an association between diseases manifesting during the follow-up period and failure of exclusively oral feeding.[6,29] In addition, it is known that oral feeding alone is not enough for adequate nutrition in some patients.[7,30]

Our age-adjusted statistical model showed a lower probability of antibiotic use, a shorter length of hospital stay, and a shorter duration of antibiotic therapy after the VFSS. These data support the conclusion that specialized care reduces respiratory morbidity in children with OPD, and this reduction plays an important role in the well-being of patients and their families. It is challenging to establish a causal relationship between aspiration and respiratory symptoms, requiring analysis of factors that are known to be difficult to single out in retrospective studies.[9] Despite some limitations and confounding factors, the relevant findings of the current study remain significant after adjustment for age, warranting further attention. The investigation

Table 3. Logistic regression model adjusted for age at the time of videofluoroscopic swallow study.

Variable	Adjusted OR (95% CI)	p
Hospitalization	0.152 (0.068-0.338)	< 0.001
Antibiotic use	2.47 (1.286-4.744)	0.007

Table 4. Difference in means adjusted for age before and after videofluoroscopic swallow study.

Variable	Before (days)	After (days)	Difference in means (95% CI)	p
Length of hospital stay*	45.96	32.77	13.19 (1.73-24.65)	0.024
Number of hospitalizations**	1.44	1.01	0.43 (0.2-0.88)	0.072
Duration of antibiotic therapy*	25.35	16.36	8.99 (1.94-16.05)	0.014

*Generalized linear model for gamma distribution. **Poisson regression.

and treatment of OPD are conducted when there is suspicion of factors not yet fully understood within the clinical context of the child. Although this does not address the methodological issues, it reinforces the importance of the data. OPD is often underrecognized as a cause of chronic respiratory symptoms,[7,15] and its respiratory presentation may be less characteristic than previously understood.[6]

The limitations of the present study include its retrospective nature, data collection from medical records, the lack of a control group, the fact that different respiratory diagnoses were related to antibiotic therapy and hospitalization, and the heterogeneity of the study population. Studies involving homogeneous populations and randomized interventions should be carried out in order to clarify the impact of OPD and its management on respiratory morbidity; to improve the quality of life of patients and their families; and to promote the standing of referral facilities, which are still lacking in most centers.

AUTHOR CONTRIBUTIONS

All authors participated in the design and planning of the study; interpretation of the findings; writing and/or revision of all preliminary drafts and the final version of the manuscript; and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Goday PS, Huh SY, Silverman A, Lukens CT, Dodrill P, Cohen SS, et al. Pediatric Feeding Disorder: Consensus Definition and Conceptual Framework. J Pediatr Gastroenterol Nutr. 2019;68(1):124-129. https://doi.org/10.1097/MPG.0000000000002188
2. Lefton-Greif MA. Pediatric dysphagia. Phys Med Rehabil Clin N Am. 2008;19(4):837-ix. https://doi.org/10.1016/j.pmr.2008.05.007
3. Bae SO, Lee GP, Seo HG, Oh BM, Han TR. Clinical characteristics associated with aspiration or penetration in children with swallowing problem. Ann Rehabil Med. 2014;38(6):734-741. https://doi.org/10.5535/arm.2014.38.6.734
4. Horton J, Atwood C, Gnagi S, Teufel R, Clemmens C. Temporal Trends of Pediatric Dysphagia in Hospitalized Patients. Dysphagia. 2018;33(5):655-661. https://doi.org/10.1007/s00455-018-9884-9
5. Bock JM, Varadarajan V, Brawley MC, Blumin JH. Evaluation of the natural history of patients who aspirate. Laryngoscope. 2017;127 Suppl 8(Suppl 8):S1-S10. https://doi.org/10.1002/lary.26854
6. Lefton-Greif MA, Carroll JL, Loughlin GM. Long-term follow-up of oropharyngeal dysphagia in children without apparent risk factors. Pediatr Pulmonol. 2006;41(11):1040-1048. https://doi.org/10.1002/ppul.20488
7. Tutor JD, Gosa MM. Dysphagia and aspiration in children. Pediatr Pulmonol. 2012;47(4):321-337. https://doi.org/10.1002/ppul.21576
8. Lefton-Greif MA, Okelo SO, Wright JM, Collaco JM, McGrath-Morrow SA, Eakin MN. Impact of children's feeding/swallowing problems: validation of a new caregiver instrument. Dysphagia. 2014;29(6):671-677. https://doi.org/10.1007/s00455-014-9560-7
9. Taniguchi MH, Moyer RS. Assessment of risk factors for pneumonia in dysphagic children: significance of videofluoroscopic swallowing evaluation. Dev Med Child Neurol. 1994;36(6):495-502. https://doi.org/10.1111/j.1469-8749.1994.tb11879.x
10. Pavithran J, Puthiyottil IV, Narayan M, Vidhyadharan S, Menon JR, Iyer S. Observations from a pediatric dysphagia clinic: Characteristics of children at risk of aspiration pneumonia. Laryngoscope. 2019;129(11):2614-2618. https://doi.org/10.1002/lary.27654
11. Krummrich P, Kline B, Krival K, Rubin M. Parent perception of the impact of using thickened fluids in children with dysphagia. Pediatr Pulmonol. 2017;52(11):1486-1494. https://doi.org/10.1002/ppul.23700
12. Morton R, Minford J, Ellis R, Pinnington L. Aspiration with dysphagia: the interaction between oropharyngeal and respiratory impairments. Dysphagia. 2002;17(3):192-196. https://doi.org/10.1007/s00455-002-0051-x
13. Kemps G, Sewitch M, Birnbaum R, Daniel SJ. Contrast pooling in videofluoroscopic swallowing study as a risk factor for pneumonia in children with dysphagia. Int J Pediatr Otorhinolaryngol. 2015;79(8):1306-1309. https://doi.org/10.1016/j.ijporl.2015.05.039
14. Casazza GC, Graham ME, Asfour F, O'Gorman M, Skirko J, Meier JD. Aspiration in the otherwise healthy Infant-Is there a natural course for improvement?. Laryngoscope. 2020;130(2):514-520. https://doi.org/10.1002/lary.27888
15. Duncan DR, Amirault J, Mitchell PD, Larson K, Rosen RL. Oropharyngeal Dysphagia Is Strongly Correlated With Apparent Life-Threatening Events. J Pediatr Gastroenterol Nutr. 2017;65(2):168-172. https://doi.org/10.1097/MPG.0000000000001439
16. American Speech-Language-Hearing Association (ASHA) [homepage on the Internet]. Rockville (MD): ASHA; c2023 [cited 2023 Nov 24]. Videofluoroscopic Swallow Study (VFSS). Available from: https://www.asha.org/practice-portal/clinical-topics/pediatric-feeding-and-swallowing/videofluoroscopic-swallow-study/
17. American Speech-Language-Hearing Association (ASHA) [homepage on the Internet]. Rockville (MD): ASHA; c2023 [cited 2023 Nov 24]. Pediatric Dysphagia. Available from: https://www.asha.org/practice-portal/clinical-topics/pediatric-dysphagia/
18. Martin-Harris B, Canon CL, Bonilha HS, Murray J, Davidson K, Lefton-Greif MA. Best Practices in Modified Barium Swallow Studies. Am J Speech Lang Pathol. 2020;29(2S):1078-1093. https://doi.org/10.1044/2020_AJSLP-19-00189
19. Benfer KA, Weir KA, Bell KL, Ware RS, Davies PSW, Boyd RN. Oropharyngeal Dysphagia and Cerebral Palsy. Pediatrics. 2017;140(6):e20170731. https://doi.org/10.1542/peds.2017-0731
20. Lawlor CM, Choi S. Diagnosis and Management of Pediatric Dysphagia: A Review. JAMA Otolaryngol Head Neck Surg. 2020;146(2):183-191. https://doi.org/10.1001/jamaoto.2019.3622
21. Jadcherla SR. Advances with Neonatal Aerodigestive Science in the Pursuit of Safe Swallowing in Infants: Invited Review. Dysphagia. 2017;32(1):15-26. https://doi.org/10.1007/s00455-016-9773-z
22. Dharmarathna I, Miles A, Allen J. Predicting penetration-aspiration through quantitative swallow measures of children: a videofluoroscopic study. Eur Arch Otorhinolaryngol. 2021;278(6):1907-1916. https://doi.org/10.1007/s00405-021-06629-4
23. Dharmarathna I, Miles A, Fuller L, Allen J. Quantitative video-fluoroscopic analysis of swallowing in infants. Int J Pediatr Otorhinolaryngol. 2020;138:110315. https://doi.org/10.1016/j.ijporl.2020.110315
24. Weir K, McMahon S, Barry L, Masters IB, Chang AB. Clinical signs and symptoms of oropharyngeal aspiration and dysphagia in children. Eur Respir J. 2009;33(3):604-611. https://doi.org/10.1183/09031936.00090308
25. Gasparin M, Schweiger C, Manica D, Maciel AC, Kuhl G, Levy DS, et al. Accuracy of clinical swallowing evaluation for diagnosis of dysphagia in children with laryngomalacia or glossoptosis. Pediatr Pulmonol. 2017;52(1):41-47. https://doi.org/10.1002/ppul.23484
26. Low J, Wyles C, Wilkinson T, Sainsbury R. The effect of compliance on clinical outcomes for patients with dysphagia on videofluoroscopy. Dysphagia. 2001;16(2):123-127. https://doi.org/10.1007/s004550011002
27. Silverio CH, Henrique CS. Evolution indicators of patients with

cerebral palsy and oropharyngeal dysphagia after therapeutic intervention. Rev Soc Bras Fonoaldiol. 2009; 14(3):381-386. https://doi.org/10.1590/S1516-80342009000300015

28. Sullivan PB, Morrice JS, Vernon-Roberts A, Grant H, Eltumi M, Thomas AG. Does gastrostomy tube feeding in children with cerebral palsy increase the risk of respiratory morbidity?. Arch Dis Child. 2006;91(6):478-482. https://doi.org/10.1136/adc.2005.084442
29. McSweeney ME, Kerr J, Amirault J, Mitchell PD, Larson K, Rosen R. Oral Feeding Reduces Hospitalizations Compared with Gastrostomy Feeding in Infants and Children Who Aspirate. J Pediatr. 2016;170:79-84. https://doi.org/10.1016/j.jpeds.2015.11.028
30. Rudolph CD, Link DT. Feeding disorders in infants and children. Pediatr Clin North Am. 2002;49(1):97-vi. https://doi.org/10.1016/S0031-3955(03)00110-X

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Clinical determinants of the modified incremental step test in adults with non-cystic fibrosis bronchiectasis

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ABSTRACT

Objectives: This study primarily aimed to investigate the clinical determinants of the Modified Incremental Step Test (MIST) in adults with non-cystic fibrosis bronchiectasis (NCFB). A secondary objective was to compare the cardiopulmonary responses after the MIST and Incremental Shuttle Walk Test (ISWT), two commonly adopted symptom-limited maximum field tests in chronic respiratory diseases. **Methods:** Forty-six patients with clinically stable bronchiectasis participated in this cross-sectional study. MIST and ISWT were performed to determine exercise capacity, while disease severity, fatigue, and quality of life were assessed using the Bronchiectasis Severity Index (BSI), the Fatigue Severity Scale (FSS), and St. George's Respiratory Questionnaire (SGRQ), respectively. Quadriceps muscle strength was evaluated using a hand-held dynamometer, walking speed with a wireless inertial sensing device, and the level of physical activity (steps/day) with a pedometer. **Results:** The BSI score, quadriceps muscle strength, daily step count, and the SGRQ total score explained 61.9% of the variance in the MIST ($p < 0.001$, $R^2 = 0.67$, $AR^2 = 0.619$). The BSI score ($r = -0.412$, $p = 0.004$), quadriceps muscle strength ($r = 0.574$, $p = 0.001$), daily step count ($r = 0.523$, $p < 0.001$), walking speed ($r = 0.402$, $p = 0.006$), FSS score ($r = -0.551$, $p < 0.001$), and SGRQ total score ($r = -0.570$, $p < 0.001$) correlated with the MIST. The patients achieved higher heart rates (HR), HR%, desaturation, dyspnea, and leg fatigue in the MIST compared to the ISWT ($p < 0.05$). **Conclusions:** Disease severity, quadriceps muscle strength, physical activity level, and quality of life were determinants of MIST. The advantages of the MIST, including higher cardiopulmonary response than ISWT and greater portability, which facilitates its use in various settings, make MIST the preferred choice for investigating symptom-limited exercise capacity in patients with NCFB.

Keywords: bronchiectasis, exercise capacity, step test, physical activity, walking speed, quality of life.

INTRODUCTION

Bronchiectasis is a chronic and progressive respiratory disease in which functional exercise capacity, quality of life, and the ability to perform daily living activities are impaired, together with pulmonary and extrapulmonary involvement.[1,2] In bronchiectasis, chronic sputum, fatigue, dyspnea symptoms, and a decline in peripheral muscle strength and endurance negatively impact functional exercise capacity.[3,4]

The most common field walking tests used to evaluate functional exercise capacity in bronchiectasis patients are the 6-minute walk test (6MWT) and the incremental shuttle walk test (ISWT).[5] Step tests offer advantages due to their greater portability compared to walking tests and the requirement for less space during application, making them suitable for use in any given environment.[6] Step tests can be either self-paced or externally paced, like the 6MWT and the ISWT. They can also be conducted with a constant or incremental workload, similar to cycle ergometer and treadmill protocols.[6] The Modified Incremental Step Test (MIST) is a symptom-limited maximum field step test that evaluates exercise capacity with gradually increasing step rates.[7] This test is reliable and responsive to pulmonary rehabilitation in individuals with stable chronic respiratory disease.[8] In bronchiectasis, MIST was assessed in only one study, and the MIST number of steps (NOSs) was highly correlated with pulmonary function, 6MWT distance, and heart rate.[7] The ISWT, the most commonly used maximum field walking test, and the MIST are valid for measuring maximum exercise capacity and have demonstrated maximum cardiopulmonary responses in individuals with bronchiectasis.[7,9] Therefore, exercise tolerance duration, cardiopulmonary stress, and effort perception in patients with bronchiectasis are comparable using the ISWT and MIST.

The determinants of exercise capacity in bronchiectasis have been previously investigated in a few studies. While the predictors of ISWT were reported as being age, body composition, respiratory function, shortness of breath, and physical activity in daily life in one study,[9] age and gender were also described in another.[10] Saint

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George's Respiratory Questionnaire (SGRQ) symptom and activity scores and high-resolution computed tomography (HRCT) score were identified as predictors of the 6MWT.[11] Although the factors limiting exercise capacity in bronchiectasis are multifactorial, they have not been explicitly studied. Considering all this information, exploring the determinants of exercise capacity in subjects with bronchiectasis is essential. In recent years, the significance of the MIST, a step test for evaluating exercise capacity in individuals with chronic pulmonary diseases, has increased; however, no studies in the literature have investigated its clinical determinants. MIST provides new opportunities to assess exercise capacity, prescribe exercise training, and reassess exercise program outcomes in environments where established field walking tests are impractical.[8] Identifying clinical and functional variables that explain MIST in bronchiectasis may serve as potential indicators for benefiting from pulmonary rehabilitation programs.

Therefore, the primary objective of this study was to determine which factors influence exercise capacity measured by MIST using different clinical and functional parameters, including disease severity, muscle strength, physical activity level, walking speed, and quality of life assessment in individuals with non-cystic fibrosis bronchiectasis (NCFB). The secondary aim was to compare the results obtained with the MIST and ISWT.

METHODS

This descriptive, cross-sectional study involved patients diagnosed with bronchiectasis who were followed up at the Department of Chest Diseases of Dokuz Eylül University, in Izmir, Turkey, between September 2019 and March 2021. The study protocol received approval from the Ethics Committee of Dokuz Eylül University (2019/18-21), and written informed consent was obtained from from all subjects. The study included individuals diagnosed with NCFB, confirmed by HRCT, who were clinically stable (no antibiotic use for four weeks) and had not participated in any regular pulmonary rehabilitation programs. Those with serious cardiac problems, neurological or orthopedic diseases, and/or malignancies were excluded.

The physical and sociodemographic characteristics of the subjects were recorded. HRCT images were obtained from their clinical records. A pulmonary function test (Sensor Medics Vmax 22, SensorMedics, Inc., Anaheim, CA, USA) was performed to measure forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), and the test was carried out following the recommended guidelines of the American Thoracic Society and the European Respiratory Society.[12]

The assessment of dyspnea perception was conducted using the Medical Research Council (MRC) dyspnea scale, a categorical scoring system ranging from 0 to 5 points. This scale involves choosing the statement most aptly representing the degree of dyspnea from five different statements about dyspnea.[13]

Disease severity was evaluated using the Bronchiectasis Severity Index (BSI). The BSI is a valid tool for identifying patients at an increased risk of future mortality, hospitalization, and exacerbations. It comprises eight parameters, which include age, body mass index (BMI), forced expiratory volume in 1s (FEV1), previous hospital admissions, the frequency of exacerbations, the score on the modified Medical Research Council (mMRC) dyspnea scale, colonization status (*Pseudomonas aeruginosa* or other organisms), and the extent of radiological findings; higher BSI scores indicate greater disease severity. According to the BSI score, disease severity can be categorized as mild (0 – 4 points), moderate (5 – 8 points), or severe (≥ 9 points).[14]

The MIST was used, as previously described, to assess exercise capacity.[7] The step test commenced at a rate of 10 steps/min, with one-step increments introduced every 30 seconds. The step rate progressed at regular intervals through auditory stimuli previously recorded on a disc.[7]

The ISWT was also administered to evaluate exercise capacity.[15] The test was conducted in an empty and quiet 10-m corridor, and walking speed was guided by an audio signal, which started at 0.5 m/s and increased progressively.

Two MISTs and ISWTs were carried out on the same day, with a resting period of at least 30 minutes between them. The second tests were performed once the participants' vital signs had returned to baseline levels to ensure consistent clinical conditions for each patient in both tests. The highest NOSs in the MIST[7] and the best distance in the ISWT were recorded.[5] Oxygen saturation and heart rate values (pulse-oximetry - Beurer PO30 Pulse Oximeter, Germany), dyspnea (Modified Borg Scale), and fatigue (Rated Perceived Exertion (RPE) Scale) were assessed before and after the tests. The tests were stopped when the participant declared inability to continue, the researcher observed that the participant was not suitable to continue the test, two consecutive beeps were missed, or SpO_2 < 80%. The reasons for stopping the tests, the total NOSs, and the test completion time were registered. The maximum heart rate (HRmax) was determined using the formula [220 – age], and the HRmax% reached at the end of the tests was calculated.[16]

Walking speed was evaluated using a wireless inertial sensing device (G-Sensor-BTS Bioengineering-S.p.A., Italy) attached to the subject's waist with a semi-elastic belt at the L4-L5 level.[17] The participants were instructed to walk along an 8-m pathway at a self-selected speed, and the walking speed was recorded in m/s.

A hand-held dynamometer (Lafayette Instrument Co., Lafayette, IN, USA) was utilized to assess quadriceps muscle strength. The measurement involved an isometric knee extension exercise at 90° of knee flexion, repeated three times, with the best value recorded in Newtons (N).[18] Percentages of muscle strength were calculated based on reference values.[19]

The level of physical activity (steps/day) was evaluated using a pedometer (CW-700, Digi-walker Pedometer, Yamax-Corp., Tokyo, Japan), a practical and suitable device for patients with bronchiectasis.[20] The pedometer was worn on the belt on the dominant side at the midline of the thigh for seven consecutive days, except during showering or swimming. The total step count in a week, walking distance (kilometers), activity duration (hours), and calories expended (kcal) were obtained from the pedometer, and the daily average values of these parameters were calculated.[21]

The Fatigue Severity Scale (FSS) was used to estimate the fatigue level of the participants.[22] In the FSS, scores ≥ 4 points indicate the presence of severe fatigue. St. George's Respiratory Questionnaire[23] was utilized to assess quality of life, as the SGRQ allows for comparisons with previous studies,[11,23] and there is strong evidence supporting its validity, internal reliability, and reproducibility.[24] The Turkish versions of the FSS and SGRQ have been validated and are cpnsidered reliable.[25,26]

Statistical analysis was performed using IBM SPSS software, version 24.0 (SPSS Inc., Chicago, IL, USA). All variables were expressed as mean ± standard deviation, frequency, and percentage when appropriate. The normality of distribution was assessed using the Skewness-Kurtosis test and histograms. When applicable, the correlation between MIST NOSs and the variables was determined via Pearson/Spearman correlation analyses. The correlation coefficients were interpreted as weak for r = 0.2-0.3, moderate for r = 0.3-0.5, and strong for r ≥ 0.5.[27] Statistical significance was set at $p < 0.05$. The paired t-test was used to compare the test results in the ISWT and MIST. Categorical data across the exercise tests were compared with the Chi-square test.

An enter regression model was developed to identify the determinants of MIST. Independent variables showing a significant correlation with MIST were included in the model. Model fit was assessed using appropriate residual and goodness-of-fit statistics.

Based on a similar study in which the predictors of ISWT were previously determined,[10] the sample size was calculated as 46 patients, considering an expected effect size of 0.727, an alpha of 0.05, and a statistical power of 0.95, using G*Power software, version 3.1.

RESULTS

A total of 48 subjects who met the inclusion criteria participated in the study. Forty-six were evaluated, and their data were analyzed (Figure 1). Twenty-six (56%) participants were female, while 20 were male. Their demographic and clinical characteristics are shown in Table 1.

The classification of disease severity among the individuals was as follows: 30 (65.2%) had mild, 10 (21.7%) had moderate, and six (13.1%) had severe bronchiectasis. The patients achieved 35% of quadriceps muscle strength as a percentage of predicted values. In addition, 25 (54.3%) patients reported experiencing severe fatigue.

Correlations between the patients' MIST NOSs and their clinical parameters can be observed in Table 2. The MIST NOSs showed a strong correlation with the ISWT distance ($r = 0.788$, $p < 0.001$), quadriceps muscle strength ($r = 0.574$, $p = 0.001$), daily number of steps ($r = 0.523$, $p < 0.001$), walking distance ($r = 0.629$, $p < 0.001$), total energy expenditure ($r = 0.528$, $p < 0.001$), FSS score ($r = -0.551$, $p < 0.001$), SGRQ total score ($r = -0.570$, $p < 0.001$), SGRQ activity score ($r = -0.541$, $p < 0.001$), and SGRQ impact score ($r = -0.525$, $p < 0.001$). Meanwhile, the MIST NOSs exhibited a moderate correlation with FEV1 (pred%) ($r = 0.456$, $p = 0.001$), FVC (pred%) ($r = 0.403$, $p = 0.005$), BSI ($r = -0.412$, $p = 0.004$), the 8-m walking speed ($r = 0.402$, $p = 0.006$), and activity duration ($r = 0.378$, $p = 0.001$).

A multiple linear regression model was used to identify the determinants of the MIST NOSs (Table 3). Our findings indicate that the BSI score ($p = 0.004$), quadriceps muscle strength ($p = 0.002$), pedometer daily number of steps ($p = 0.039$), and SGRQ total score ($p = 0.003$) explained the variance in the MIST NOSs by 61.9% [$F = 13.190$, $p < 0.001$, $R^2 = 0.67$, $AR^2 = 0.619$].

ISWT and MIST performance, physiological responses, and the exercise perception of the patients are presented in Table 4. No differences were observed in resting values of HR, dyspnea, or leg fatigue between the ISWT and MIST ($p > 0.05$). SpO_2 at rest was significantly higher before MIST than ISWT ($p = 0.038$, 96.58 ± 1.32 vs. 96.26 ± 1.55, respectively). Changes in HR, dyspnea, and leg fatigue parameters during the MIST were significantly higher compared to the ISWT ($p < 0.001$). While 64% of HRmax was reached in the ISWT, 82% was reached in the MIST. Three participants

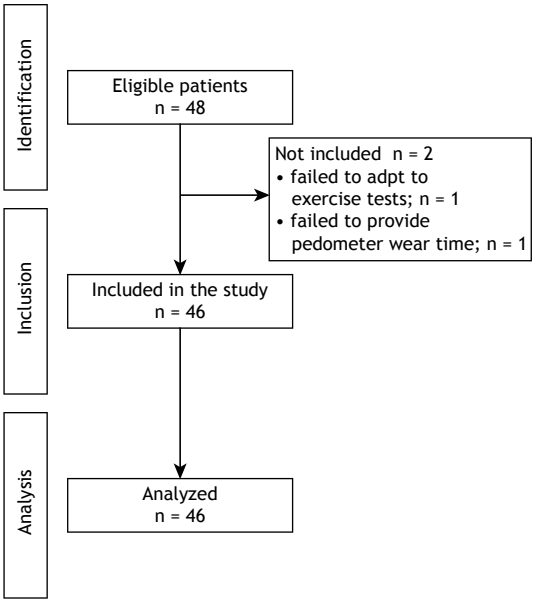

Figure 1. Study enrollment flowchart.

Table 1. Demographic and clinical features of individuals with bronchiectasis.

Variables	Mean (SD)	Range
Age (years)	59.30 (7.72)	41 - 74
Body weight (kg)	73.98 (12.59)	48 - 97
Body mass index (kg/m^2)	27.93 (4.41)	20.20 - 37.90
Fat-free mass (kg)	51.12 (10.29)	30.80 - 74.40
Disease duration (years)	13.43 (11.36)	1 - 50
Smoking history (pack-years)	10.28 (21.25)	0 - 120
Etiology, n (%)		
Idiopathic	16 (35)	-
Post-infectious problems	12 (27)	-
Autoimmune diseases	9 (19)	-
Respiratory disease (asthma, COPD)	9 (19)	-
Other reasons (toxic inhalation)		
Medication use, n (%)		
Inhaled bronchodilator	21 (45.65)	-
Inhaled corticosteroid	7 (15.21)	-
Mucolytics	4 (8.69)	-
Antihypertensive	10 (21.73)	-
Glucose-lowering medication	4 (8.69)	-
Lipid-modifying medication	2 (4.34)	-
FEV1 (pred%)	75.58 (19.13)	27 - 110
FVC (pred%)	81.04 (17.89)	41 - 118
MRC score	1.71 (0.54)	1 - 3
BSI score	4.5 (2.68)	2 - 12
8-m gait speed (m/s)	1.16 (0.16)	0.86 - 1.63
Quadriceps (N)	122.54 (24.46)	77.47 -180.44
Number of steps (steps/day)	6,418.74 (2,225.30)	2,813.00 -11,479.00
Walking distance (km/day)	3.94 (1.58)	1.54 - 7.48
Energy expenditure (kcal/day)	260.16 (117.76)	92.94 -626.47
Total physical activity duration (min/day)	67.8 (21.00)	31.2 - 112.8
Fatigue Severity Scale score	5.45 (3.22)	2.25 - 12.75
SGRQ total	32.36 (12.40)	9.36 - 63.67
SGRQ symptom	40.86 (16.53)	0.00 - 76.23
SGRQ activity	44.02 (15.79)	11.16 - 79.79
SGRQ impact	22.51 (14.28)	4.51 - 64.09

N = 46 subjects; values shown as mean (SD); MRC = Medical Research Council Dyspnea Scale; BSI = Bronchiectasis Severity Index; SGRQ = St. George's Respiratory Questionnaire; FEV1 = Forced Expiratory Volume in 1s; FVC = Forced Vital Capacity.

(6%) in the ISWT and 27 (59%) in the MIST reached HRmax and completed the tests. Changes in SpO_2 between rest and exercising ≥4% were considered desaturation. All subjects showing desaturation in the ISWT also exhibited desaturation in the MIST.

DISCUSSION

This study is the first to investigate the determinants of exercise capacity with the MIST in individuals with bronchiectasis using different clinical and functional parameters. Disease severity, peripheral muscle strength, physical activity level, walking speed, fatigue, and quality of life were found to be related to the MIST NOSs. Disease severity, peripheral muscle strength, physical activity level, and quality of life were identified as determinants of MIST. Also, patients achieved higher HR, HR%, desaturation rates, dyspnea, and leg fatigue in the MIST compared to the ISWT.

Corroborating the findings of previous studies, we noted a decrease in exercise capacity in the ISWT in subjects with bronchiectasis.[10,28–31] Only one study evaluated exercise capacity with the MIST in individuals with bronchiectasis. Although the HR values, mean NOSs, and test duration during peak exercise herein were similar to those reported in a previous study,[7] the SpO_2 (%) and dyspnea scores differed. These discrepancies may be attributed to the better respiratory function of the subjects in the present study. Disease severity was not evaluated in the previous study,[7] hindering our ability to make comparisons.

To our knowledge, no studies in the literature have explored the relationship between MIST and ISWT results in individuals with bronchiectasis. Considering that both tests are valid for measuring maximum exercise capacity in subjects with bronchiectasis and elicit maximum cardiopulmonary responses, it is possible to compare patient performance in both

Table 2. Univariate analysis of the variables and the MIST number of steps.

Variables	MIST NOSs	
	r	*P*
Age (years)	-0.290†	0.050
Gender	0.008‡	0.957
Height (m)	0.137†	0.364
Body weight (kg)	0.100†	0.508
Body mass index (kg/m^2)	0.024†	0.873
Fat-free mass (kg)	0.195†	0.195
Disease duration (years)	-0.193‡	0.198
Smoking history (pack-years)	0.092‡	0.542
FEV1 (pred%)	0.456†	0.001*
FVC (pred%)	0.403†	0.005*
BSI score	-0.412 ‡	0.004*
ISWT distance (m)	0.788†	<0.001*
8-m gait speed (m/s)	0.402†	0.006*
Quadriceps (N)	0.574†	<0.001*
Number of steps (steps/day)	0.523†	<0.001*
Walking distance (km/day)	0.629†	<0.001*
Energy expenditure (kcal/day)	0.528†	<0.001*
Total physical activity duration (min/day)	0.378†	0.001*
Fatigue Severity Scale score	-0.551‡	<0.001*
SGRQ total	-0.570†	<0.001*
SGRQ symptom	-0.190†	0.206
SGRQ activity	-0.541†	<0.001*
SGRQ impact	-0.525‡	<0.001*

N = 46 subjects; ISWT = Incremental Shuttle Walk Test; MIST = Modified Incremental Step Test; MRC = Medical Research Council Dyspnea Scale; BSI = Bronchiectasis Severity Index; SGRQ = St. George's Respiratory Questionnaire; FEV1 = Forced Expiratory Volume in 1s, FVC = Forced Vital Capacity; NOSs = Number of steps; * $p < 0.05$; †Pearson r, ‡Spearman rho.

tests. The HRmax% value achieved in the MIST was higher compared to the ISWT (82% vs. 64%), with more participants reaching HRmax (n = 27 vs. n = 3) and completing the test. Although the ISWT is widely used in studies involving bronchiectasis patients,[3,10] based on these results, the MIST is more effective at increasing heart rate than the ISWT. The increase in the MIST at more frequent intervals may have accelerated the heart rate in patients with higher functional capacity. Therefore, the MIST may be a more useful exercise test than the ISWT for individuals with high functional capacity. Moreover, the step test has an advantage over the walking test in terms of portability and applicability in smaller spaces, making it suitable for situations lacking adequate space for the maximum walking field test.

Fatigue is observed in 74% of patients with bronchiectasis,[32] resulting in impaired exercise tolerance.[11] The FSS score showed a strong correlation with the MIST NOSs, consistent with the results obtained in a previous study[11] that reported an association between physical fatigue and reduced exercise tolerance in bronchiectasis. Due to the continuous vertical displacement of the body during the step test, the workload of the muscles increases, causing fatigue and desaturation.[33] While fatigue is not reported as a limitation in walking tests, it is considered as a limiting symptom in tests involving stairs or step activities.[34] More subjects in the MIST ended the test due to leg fatigue than in the ISWT. Studies involving bronchiectasis have shown that quadriceps muscle strength decreases and affects exercise capacity.[4,28,30] In the present study, quadriceps muscle strength strongly correlated with exercise capacity and can be a predictor of exercise capacity. Desaturation has been observed in step tests in studies analyzing different pulmonary diseases.[35,36] Here, desaturation was observed more in individuals with different levels of disease severity in the MIST compared to the ISWT, indicating that the step test is more sensitive to desaturation. This finding is consistent with another study[33] in which desaturation was more prevalent in the MIST than in the cardiopulmonary exercise test (CPET) in patients with COPD.[33]

Individuals with bronchiectasis often perceive dyspnea, which significantly affects exercise capacity.[4,9] While dyspnea was reported as the primary reason for ending the MIST, this was not reported in the ISWT. More subjects ended the test due to leg fatigue in the MIST than in the ISWT. When the responses to the two exercise tests were evaluated regarding leg fatigue and dyspnea, the step test was identified as the most symptom-limiting test according to the participants. Hence, this test better reflects the cardiopulmonary responses and symptoms in the face of increased workload. Exercise tests applied at an incremental rate

Table 3. Multiple linear regression analysis of variables associated with the MIST number of steps.

Independent variables	B	SE	95% CI	t	p
Constant	86.932	49.436	-13.092 to 186.895	1.758	0.087
BSI score	-6.028	1.971	-10.015 to 2.041	-3.058	0.004*
Quadriceps (N)	8.447	0.2504	3.381 to 13.512	3.381	0.002*
Number of steps (steps/day)	0.006	0.003	0.00 to 0.012	2.138	0.039*
SGRQ total	-1.75	0.551	-2.865 to -0.635	-3.174	0.003*

*p < 0.05; t = statistical test; B = unstandardized regression coefficient; SE = standard error; BSI = Bronchiectasis Severity Index; SGRQ = St. George's Respiratory Questionnaire.

Table 4. Variables at Peak Exercise in the ISWT and MIST.

Variables	ISWT	MIST	95% CI	p
Outcome	401.67 (73.65) meters	152.93 (55.00) steps	-	-
Time, min	6.86 (0.80)	8.36 (2.02)	-116.42 to -6.92	< 0.001*
SpO_2, %	95.45 (3.69)	95.13 (3.83)	-0.87 to 0.22	0.238
Δ SpO_2	- 0.8 (3.12)	1.45 (3.03)	-1.20 to -0.10	0.021*
Δ SpO_2 ≥ 4%, n	4 (2 moderate, 2 severe)	7 (1 mild, 4 moderate, 2 severe)	-	< 0.001*
Heart rate, beats/min	102.06 (16.35)	132.02 (19.90)	24.29 to 35.62	< 0.001*
Heart rate, % maximum predicted	63.60 (10.54)	82.15 (11.70)	21.97 to 10.90	< 0.001*
Dyspnea	1.67 (1.30)	3.21 (1.47)	1.05 to 2.03	< 0.001*
Leg fatigue	6.85 (6.52)	12.19 (2.76)	-11.17 to -9.67	< 0.001*
Reasons for ending the test				
SpO_2 < 80%, n (%)	-	2 (4.34)	-	-
Leg fatigue, n (%)	4 (8.69)	15 (32.60)	-	-
Dyspnea, n (%)	-	4 (8.69)	-	-
Leg fatigue and dyspnea, n (%)	-	7 (15.21)	-	-

N = 46 subjects; ISWT = Incremental Shuttle Walk Test; MIST = Modified Incremental Step Test; values expressed as mean (SD) * p < 0.05 between tests.

or workload in healthy individuals are recommended to last 8-12 minutes.[37] The mean duration of the MIST was 8.36 minutes, while that of the ISWT was 6.86 minutes. This result meets the recommended minimum time to observe the maximum cardiopulmonary responses during peak exercise, which is 8 minutes, indicating that the step test is well-tolerated.

We found that high BSI scores are moderately associated with a decrease in exercise capacity, and that the BSI score is a determinant of MIST. A limited number of studies have evaluated the effect of disease severity on exercise capacity in bronchiectasis. One previous study reported that patients with moderate-to-severe disease significantly achieved lower walking distance values than those with mild bronchiectasis.[38] In the present study, as the distribution of participants according to disease severity classification was not homogeneous, no comparisons were made between groups in terms of exercise capacity. However, a moderate negative correlation was found between disease severity and exercise capacity, consistent with the literature.

The decrease in walking speed in subjects with chronic lung disease is associated with general health status and reflects the multisystemic effects of the disease besides impairments in pulmonary function.[39] In COPD, walking speed has been associated with exercise capacity.[39,40] The only study evaluating walking speed in bronchiectasis found no relationship between 4-meter gait speed and sedentary behavior duration.[38] In this study, we assessed walking speed in bronchiectasis using an objective device and found a moderate correlation between walking speed and exercise capacity.

Furthermore, we identified a relationship between physical activity level and the MIST NOSs in bronchiectasis, with the former being a determinant of MIST. The daily step count of the participants was less than the minimum value of 7,000 steps/day.[21] Our results support studies that reported that the physical activity level of subjects with bronchiectasis decreased and is associated with exercise capacity.[28–30]

The strong association between the MIST and SGRQ activity, impact, and total scores is consistent with previous studies investigating the relationship between exercise capacity and SGRQ in bronchiectasis.[11,23] The SGRQ symptom domain assesses the frequency, severity, and duration of symptoms, while the activity domain analyzes the physical limitations and impairments associated with respiratory symptoms.[23] Therefore, there may be a lack of correlation between the SGRQ symptom domain and exercise capacity, given the disease severity was mild/moderate. In addition, the correlation between the SGRQ activity score and the MIST in our study may be explained by the low levels of physical activity in our patients. It is not unexpected that the SGRQ total score is a predictor of MIST. However, our study supports the view that

physical limitations, as well as respiratory signs and symptoms, are clinically relevant when assessing exercise capacity in patients with mild-to-moderate bronchiectasis.

The present study had some limitations. Firstly, gas exchange parameters could not be measured during the exercise tests due to equipment requirements. During the step test, which is favored in clinical practice due to its ease of use and low cost, the participants reached the maximum predicted heart rates, estimated using the formula [220 – age], and the exercise test was considerably successful. We compared the ISWT and MIST test responses, but not gas exchange parameters. Secondly, both maximum tests were performed on the same day. However, sufficient rest intervals were provided between tests. The tests were conducted a second time when the participants' vital signs returned to baseline levels to ensure the same clinical conditions were maintained for each patient in both tests. Finally, we used a pedometer to assess physical activity levels instead of an accelerometer, which offers a more precise measurement of physical activity intensity. Nevertheless, both accelerometers and pedometers are viable tools for assessing physical activity in individuals with bronchiectasis by tracking daily step counts.[20]

In conclusion, disease severity, quadriceps muscle strength, physical activity levels, and quality of life were independently related to exercise capacity. Although the ISWT is one of the most widely used field tests, the MIST can be preferred to evaluate the exercise capacity of patients with bronchiectasis due to its advantages in generating greater cardiopulmonary responses and requiring less space than the ISWT. Exercise intensity can be calculated, and exercise prescription can be planned by estimating the workload[6] or oxygen consumption[33] with the number of steps taken, which is one of the MIST outcome parameters.

AUTHOR CONTRIBUTIONS

MMB: Investigation, Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing; SS: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision; AT: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing; BOK: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing; DG: Conceptualization, Methodology, Resources; CS: Conceptualization, Methodology, Writing - Review & Editing, Resources, Supervision.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50(3):1700629. https://doi.org/10.1183/13993003.00629-2017.
2. Pasteur MC, Bilton D, Hill AT. British Thoracic Society Bronchiectasis non-CF Guideline Group. British thoracic society guideline for non-CF bronchiectasis. Thorax. 2010 Jul 1;65(SUPPL. 1):i1-58. https://doi.org/10.1136/thx.2010.136119.
3. Lee AL, Cecins N, Holland AE, Hill CJ, McDonald CF, Burge AT, et al. Field Walking Tests Are Reliable and Responsive to Exercise Training in People With Non-Cystic Fibrosis Bronchiectasis. J Cardiopulm Rehabil Prev. 2015;35(6):439-45. https://doi.org/10.1097/HCR.0000000000000130.
4. Ozalp O, Inal-Ince D, Calik E, Vardar-Yagli N, Saglam M, Savci S, et al. Extrapulmonary features of bronchiectasis: muscle function, exercise capacity, fatigue, and health status. Multidiscip Respir Med. 2012;7(1):3. https://doi.org/10.1186/2049-6958-7-3.
5. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-46. https://doi.org/10.1183/09031936.00150314.
6. De Andrade CH, De Camargo AA, De Castro BP, Malaguti C, Dal Corso S. Comparison of cardiopulmonary responses during 2 incremental step tests in subjects with COPD. Respir Care. 2012;57(11):1920-6. https://doi.org/10.4187/respcare.01742.
7. Camargo AA, Lanza FC, Tupinambá T, Corso SD. Reproducibility of step tests in patients with bronchiectasis. Braz J Phys Ther. 2013;17(3):255-62. https://doi.org/10.1590/S1413-35552012005000089.
8. Burge AT, Rodrigues JC Jr, Abramson MJ, Cox NS, Bondarenko J, Webb E, et al. Application of the Modified Incremental Step Test for Pulmonary Rehabilitation. Phys Ther. 2021;101(5):pzab044. https://doi.org/10.1093/PTJ/PZAB044.
9. De Camargo AA, Amaral TS, Rached SZ, Athanazio RA, Lanza FC, Sampaio LM, et al. Incremental shuttle walking test: a reproducible and valid test to evaluate exercise tolerance in adults with noncystic fibrosis bronchiectasis. Arch Phys Med Rehabil. 2014;95(5):892-9. https://doi.org/10.1016/j.apmr.2013.11.019.
10. Yildiz S, Inal-Ince D, Calik-Kutukcu E, Vardar-Yagli N, Saglam M, Arikan H, et al. Clinical Determinants of Incremental Shuttle Walk Test in Adults with Bronchiectasis. Lung. 2018;196(3):343-9. https://doi.org/10.1007/s00408-018-0094-x.
11. Lee AL, Button BM, Ellis S, Stirling R, Wilson JW, Holland AE, et al. Clinical determinants of the 6-Minute Walk Test in bronchiectasis. Respir Med. 2009;103(5):780-5. https://doi.org/10.1016/j.rmed.2008.11.005.
12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. https://doi.org/10.1183/09031936.05.00034805.
13. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-6. https://doi.org/10.1136/thx.54.7.581.
14. Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576-85. https://doi.org/10.1164/rccm.201309-1575OC.
15. Cartlidge MK, Smith MP, Bedi P, Donaldson S, Clarke A, Mantoani LC, et al. Validation of the Incremental Shuttle Walk Test as a Clinical End Point in Bronchiectasis. Chest. 2018;154(6):1321-9. https://doi.

org/10.1016/j.chest.2018.09.019.

16. Fox EL, Bowers RW, Foss ML. The physiological basis of physical education and athletics. William C. Brown Publication: Philadelphia; 1988:734. p. 435. Disponível em: https://books.google.com.tr/books/about/The_Physiological_Basis_of_Physical_Educ.html?id=b0NOAQAAIAAJ&redir_esc=y.
17. Awotidebe TO, Ativie RN, Oke KI, Akindele MO, Adedoyin RA, Olaogun MO, et al. Relationships among exercise capacity, dynamic balance and gait characteristics of Nigerian patients with type-2 diabetes: an indication for fall prevention. J Exerc Rehabil. 2016;12(6):581-8. https://doi.org/10.12965/jer.1632706.353.
18. Bohannon RW. Test-Retest Reliability of Hand-Held Dynamometry During a Single Session of Strength Assessment. Phys Ther. 1986;66(2):206-9. https://dx.doi.org/10.1093/ptj/66.2.206.
19. Andrews AW, Thomas MW, Bohannon RW. Normative Values for Isometric Muscle Force Measurements Obtained With Hand-held Dynamometers. Phys Ther. 1996;76(3):248-59. https://doi.org/10.1093/ptj/76.3.248.
20. O'Neill B, McDonough SM, Wilson JJ, Bradbury I, Hayes K, Kirk A, et al. Comparing accelerometer, pedometer and a questionnaire for measuring physical activity in bronchiectasis: a validity and feasibility study? Respir Res. 2017;18(1):16. https://doi.org/10.1186/s12931-016-0497-2.
21. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act. 2011;8:79. https://doi.org/10.1186/1479-5868-8-79.
22. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3. https://doi.org/10.1001/archneur.1989.00520460115022.
23. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. Am J Respir Crit Care Med. 1997;156(2 Pt I):536-41. https://doi.org/10.1164/ajrccm.156.2.9607083.
24. Spinou A, Fragkos KC, Lee KK, Elston C, Siegert RJ, Loebinger MR, et al. The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. Thorax. 2016;71(8):683-94. https://doi.org/10.1136/thoraxjnl-2015-207315.
25. Polatli M, Yorgancioğlu A, Aydemir Ö, Yilmaz Demirci N, Kirkil G, Atiş Nayci S, et al. St. George solunum anketinin Türkçe geçerlilik ve güvenilirliği. Tuberkuloz ve Toraks. 2013;61(2):81-7. Disponível em: https://toad.halileksi.net/wp-content/uploads/2022/07/st-george-solunum-anketi-toad.pdf.
26. Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res. 2007;30(1):81-5. https://doi.org/10.1097/MRR.0b013e3280146ec4.
27. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2. ed. New York: Academic Press; 2013. 567 p.
28. De Camargo AA, Boldorini JC, Holland AE, De Castro RA, Lanza FC, Athanazio RA, et al. Determinants of Peripheral Muscle Strength and Activity in Daily Life in People With Bronchiectasis. Phys Ther. 2018;98(3):153-161. https://doi.org/10.1093/ptj/pzx123.
29. José A, Ramos TM, De Castro RA, De Oliveira CS, De Camargo AA, Athanazio RA, et al. Reduced Physical Activity With Bronchiectasis. Respir Care. 2018;63(12):1498-1505. https://doi.org/10.4187/respcare.05771.
30. Cakmak A, Inal-Ince D, Sonbahar-Ulu H, Bozdemir-Ozel C, Ozalp O, Calik-Kutukcu E, et al. Physical activity of patients with bronchiectasis compared with healthy counterparts: A cross-sectional study. Heart Lung. 2020;49(1):99-104. https://doi.org/10.1016/j.hrtlng.2019.09.004.
31. Probst VS, Hernandes NA, Teixeira DC, Felcar JM, Mesquita RB, Gonçalves CG, et al. Reference values for the incremental shuttle walking test. Respir Med. 2012;106(2):243-8. https://doi.org/10.1016/j.rmed.2011.07.023.
32. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med. 2006;100(12):2183-9. https://doi.org/10.1016/j.rmed.2006.03.012.
33. Dal Corso S, De Camargo AA, Izbicki M, Malaguti C, Nery LE. A symptom-limited incremental step test determines maximum physiological responses in patients with chronic obstructive pulmonary disease. Respir Med. 2013;107(12):1993-9. https://doi.org/10.1016/j.rmed.2013.06.013.
34. Dreher M, Walterspacher S, Sonntag F, Prettin S, Kabitz HJ, Windisch W. Exercise in severe COPD: is walking different from stair-climbing? Respir Med. 2008;102(6):912-8. https://doi.org/10.1016/j.rmed.2008.01.002.
35. Hadeli KO, Siegel EM, Sherrill DL, Beck KC, Enright PL. Predictors of oxygen desaturation during submaximal exercise in 8,000 patients. Chest. 2001;120(1):88-92. https://doi.org/10.1378/chest.120.1.88.
36. Dal Corso S, Duarte SR, Neder JA, Malaguti C, De Fuccio MB, De Castro Pereira CA, et al. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29(2):330-6. https://doi.org/10.1183/09031936.00094006.
37. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(10):1451. https://doi.org/10.1164/ajrccm.167.10.950.
38. McKeough ZJ, Large SL, Spencer LM, Cheng SW, McNamara RJ. An observational study of self-reported sedentary behaviour in people with chronic obstructive pulmonary disease and bronchiectasis. Braz J Phys Ther. 2020;24(5):399-406. https://doi.org/10.1016/j.bjpt.2019.05.005.
39. Karpman C, Benzo R. Gait speed as a measure of functional status in COPD patients. Int J Chron Obstruct Pulmon Dis. 2014;9:1315-20. https://doi.org/10.2147/COPD.S54481.
40. DePew ZS, Karpman C, Novotny PJ, Benzo RP. Correlations between gait speed, 6-minute walk distance, physical activity, and self-efficacy in patients with severe chronic lung disease. Respir Care. 2013;58(12):2113-9. https://doi.org/10.4187/respcare.02471.

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ORIGINAL ARTICLE

Vaccination status and outcomes in critical COVID-19 patients

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ABSTRACT

Objective: To analyze the clinical characteristics and outcomes of patients with COVID-19–related acute respiratory failure on the basis of their vaccination status at the time of ICU admission. **Methods:** We conducted a retrospective observational study using a prospective database of patients admitted to the ICU of a university hospital in the city of Murcia, in Spain, between January 1, 2021 and September 1, 2022. Clinical, analytical, and sociodemographic data were collected and analyzed on the basis of patient vaccination status. We adjusted for confounding variables using propensity score matching and calculated adjusted ORs and 95% CIs. **Results:** A total of 276 patients were included in the study. Of those, 8.3% were fully vaccinated, 12% were partially vaccinated, and 79.7% were unvaccinated. Although fully vaccinated patients had more comorbidities, partially vaccinated patients had higher disease severity. The proportion of patients with severe acute respiratory failure was higher in the unvaccinated group, followed by the partially vaccinated group. No significant differences were found among the different groups regarding complications, duration of ventilatory support, or length of ICU/hospital stay. In the sample selected by propensity score matching, the number of patients with severe complications and the in-hospital mortality rate were higher in unvaccinated patients, but the differences were not significant. **Conclusions:** This study failed to show a significant improvement in outcomes in critically ill COVID-19 patients vaccinated against SARS-CoV-2. However, the CIs were wide and the mortality point estimates favored patients who received at least one dose of COVID-19 vaccine.

Keywords: COVID-19; Vaccination; Critical care.

INTRODUCTION

Since the onset of the COVID-19 pandemic, successive epidemic waves have been primarily managed by social isolation measures and widespread adoption of barrier precautions to prevent transmission of SARS-CoV-2.[1] Toward the end of 2020, different vaccines were introduced with the aim of preventing transmission and mitigating the severity of disease.[2,3] Disease severity can be evaluated by the extent of pneumonia on chest CT scans,[4,5] need for hospital and/or ICU admission, need for respiratory support, and mortality.[6-11] Several meta-analyses have shown a relationship between vaccination and a reduction in disease severity, but the evidence regarding the effect of vaccination on viral transmission is less robust.[9-11] Messenger RNA vaccines have been the most administered around the world, and, despite their imperfect efficacy in preventing viral transmission, they have been associated with reductions in hospitalization, ICU admission, and mortality, although the underlying mechanisms have yet to be fully understood.[12]

The role of prior vaccination in patients presenting with critical COVID-19 and requiring ICU admission or developing ARDS is less clear. Several studies have analyzed the outcomes of ICU patients on the basis of their vaccination status, but the results are conflicting.[13-16] In a multicenter study conducted in Greece and involving 256 patients with ARDS, mortality was found to be lower in fully vaccinated individuals.[14] In a study conducted in an ICU in Spain, full vaccination was associated with fewer complications and lower mortality, although the differences were not significant.[13] In contrast, no difference in mortality was found between vaccinated and unvaccinated patients in multicenter studies conducted in Italy[15] and in Australia.[16] All of the aforementioned studies were conducted between June of 2021 and February of 2022, when the predominant SARS-CoV-2 variants were the Delta and then the Omicron. Comparison of results across studies is hindered by different classifications of vaccination status and the exclusion of patients with incomplete vaccination status in some studies.[15]

The objective of this study was to analyze the clinical characteristics and outcomes of patients with COVID-19–related acute respiratory failure (ARF) on the basis of their vaccination status at the time of ICU admission.

METHODS

We conducted a retrospective observational study using a prospective database of patients admitted to the

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ICU of a university hospital in the city of Murcia, in Spain. The study was approved by the local research ethics committee.

Patients

Our study included all patients ≥ 18 years of age consecutively admitted to the ICU between January 1, 2021 and September 1, 2022 because of COVID-19–related ARF. Diagnostic criteria included microbiological confirmation of COVID-19—a positive RT-PCR test (REALQUALITY RQ-2019-nCoV; AB ANALITICA s.r.l., Padova, Italy, or QuantiTect Probe RT-PCR Kit; QIAGEN, Hilden, Germany)—and the presence of pulmonary infiltrates on imaging.

Initial respiratory support was tailored to patient clinical status. High-flow nasal cannula oxygen therapy was preferentially used in patients with an RR of < 25 breaths/min and a PaO_2/FiO_2 ratio of 150-200 mmHg. In cases of severe hypoxemia (PaO_2/FiO_2 < 150 mmHg), noninvasive positive-pressure ventilation, particularly CPAP, was the approach of choice. Noninvasive ventilation (NIV) was delivered by VISION® and V60® ventilators (Philips Respironics, Murrysville, PA, USA). CPAP was initiated at a pressure of 10 cmH_2O and, if needed, progressively titrated up to 15 cmH_2O. When BiPAP was selected, the starting expiratory positive airway pressure (EPAP) was also set at 10-15 cmH_2O, the inspiratory positive airway pressure not exceeding the EPAP level by more than 5 cmH_2O. A full face mask was the interface of choice when initiating ventilatory support. Endotracheal intubation and invasive mechanical ventilation were the primary interventions used in order to prevent imminent cardiorespiratory arrest. Regardless of the respiratory support, the goal was to maintain an SpO_2 of 92-96% in cases of hypoxemic ARF and an SpO_2 of 88-92% in cases of hypercapnic ARF. For patients undergoing NIV, fentanyl was routinely administered to enhance tolerability. However, there were instances in which it became necessary to switch to another medication or supplement it with sedatives or neuroleptics, particularly in the presence of persistent intolerance or delirium. Protective ventilation settings and periodic prone positioning were used in patients undergoing endotracheal intubation and invasive mechanical ventilation.

Study variables and statistical analysis

Clinical and analytical data were collected at admission and during hospitalization. Sociodemographic variables, clinical variables (i.e., patient-reported signs and symptoms), and analytical variables were analyzed. Clinical status and disease severity were determined by the Simplified Acute Physiology Score II at admission[17] and the daily SOFA score.[18] Comorbidity burden was assessed by the Charlson Comorbidity Index.[19]

The COVID-19 waves were as follows: 1st wave, from November 3, 2020 to April 23, 2020; 2nd wave, from August 13, 2020 to December 8, 2020; 3rd wave, from December 23, 2020 to March 24, 2021; 4th wave, from April 6, 2021 to May 26, 2021; 5th wave, from July 9, 2021 to October 29, 2021; and 6th wave, from November 9, 2021 to March 23, 2022. After the 6th wave, there were only sporadic COVID-19 cases.

The main patient-related variables are detailed in Table S1 in the supplementary material. The primary outcomes of the study were in-hospital mortality and complications related to COVID-19 and the respiratory support used. We analyzed the following complications: hyperglycemia (≥ two consecutive blood glucose measurements ≥ 180 mg/dL and requiring insulin); severe bleeding (a drop of ≥ 2 g/L in the hemoglobin level); acute kidney injury (a ≥ 1.5-fold increase in creatinine levels from baseline accompanied by oliguria); agitation/hyperactive delirium (acute and fluctuating disturbance of consciousness and cognitive functions associated with muscle hyperactivity requiring medication for control); muscle weakness acquired in the ICU (electromyography showing critical illness polyneuropathy or myopathy); thromboembolic disease (one or more episodes of deep vein thrombosis or pulmonary embolism); atrial fibrillation (not present at admission); stroke (sustained neurological deficit caused by cerebral ischemic or hemorrhagic disease); barotrauma (presence of air in the pleural cavity or mediastinum during respiratory support); and nosocomial infection (catheter-related bloodstream infection, nosocomial pneumonia, or urinary tract infection).

Patients were categorized on the basis of their vaccination status at the time of infection with SARS-CoV-2, as follows: a) complete vaccination—patients who had received the required dose or doses of vaccine, including a booster dose or doses (if approved by health authorities), and who developed COVID-19 between 14 days and 5 months after the last dose; b) incomplete vaccination—patients who did not receive all recommended doses of vaccine, including a booster dose or doses if approved, or who developed COVID-19 less than 14 days or more than 5 months after the last dose; and c) no vaccination—patients who did not receive any COVID-19 vaccine. We determined vaccination status and type of administered vaccine (if any) using a web-based database available in the autonomous community of Murcia, in Spain.

Three types of comparisons were made. First, all three groups of patients were compared on the basis of their vaccination status (complete vaccination, incomplete vaccination, or no vaccination). Second, incompletely vaccinated patients and unvaccinated patients were grouped together and compared with fully vaccinated patients. Finally, patients with complete vaccination and those with incomplete vaccination were also grouped together and compared with those who did not receive any vaccination.

Quantitative variables are presented as mean ± standard deviation or median (interquartile range), whereas qualitative variables are presented as

absolute and relative frequencies. Comparisons between qualitative variables were performed with Pearson's chi-square test or Fisher's exact test. For comparisons between quantitative and qualitative variables with two categories, the Student's t-test or the Mann-Whitney test was employed. If a qualitative variable had three or more categories, comparisons were made by ANOVA or the Kruskal-Wallis test. Further analysis comparing unvaccinated patients and those who received at least one dose of vaccine was performed by means of propensity score matching (1:1 matching without replacement), matching within calipers being defined by the propensity score. The variables used for matching were present before the onset of COVID-19 and were selected to better assess the relationship between vaccination status and prognosis. They included age, sex, obesity, wave of the COVID-19 pandemic (grouping together patients admitted during waves 3 and 4, and those admitted during waves 5, 6, and later), the Charlson Comorbidity Index, and immunosuppression status. A caliper width of 0.1 of the standard deviation of the logit of the propensity score was used for the matching process. To assess the effectiveness of propensity score matching in minimizing differences between patients with and without vaccination, standardized mean differences were computed for each variable before and after matching. Standardized mean differences of < 10% were considered indicative of successful propensity score matching and balance between the two groups. Postmatching group comparisons were performed with the Student's t-test for paired data, the Wilcoxon test, or McNemar's test. Adjusted ORs and 95% CIs were calculated.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 25 (IBM Corporation, Armonk, NY, USA). All tests were two-tailed, and the level of significance was set at $p \leq 0.05$.

RESULTS

Between the start of the COVID-19 pandemic and September of 2022, 465 patients with positive RT-PCR results for SARS-CoV-2 were admitted to the ICU. Of those, 189 were excluded from the study. A flow chart of patient selection is shown in Figure S1. A total of 276 patients were included in the study. Of those, 204 (73.9%) were male, with a mean age of 58.8 ± 13.8 years. Of the 276 patients included in the study, 23 (8.3%) received complete vaccination and 33 (12%) received incomplete vaccination, whereas 220 (79.7%) did not receive any vaccination. Of the 33 patients with incomplete vaccination, 12 did not receive any booster that they were due to receive, 2 developed disease within two weeks of receiving the second dose of vaccine, and 19 developed disease more than 5 months after the last dose. The type of vaccine and number of doses received in the vaccinated groups are shown in Table 1.

Sociodemographic, background, and clinical characteristics of patients

As can be seen in Table 2, age was the only sociodemographic characteristic that differed among the three groups of patients ($p = 0.009$). Although patients with complete vaccination had more comorbidities, as assessed by the Charlson Comorbidity Index ($p < 0.001$), disease severity was higher in the incomplete vaccination group, followed by the complete vaccination and unvaccinated groups ($p < 0.001$). Dyspnea at diagnosis was less common in the fully vaccinated group ($p = 0.009$). These results held when we compared fully and partially vaccinated patients with unvaccinated patients, the exception being dyspnea, which did not differ significantly between the two groups.

First-line and further respiratory support did not differ among any of the groups. However, serum levels of D-dimer and LDH were significantly higher in the unvaccinated group, as opposed to C-reactive protein levels, which were higher in fully and partially vaccinated patients (Table 3). Although neither RR nor PaO_2/FiO_2 differed in the comparisons made, the proportion of patients with more severe ARF ($PaO_2/FiO_2 < 100$) was higher in unvaccinated patients, followed by partially vaccinated patients ($p = 0.045$). None of the variables related to respiratory/ventilatory pressures, EPAP/CPAP, PEEP, plateau pressure, or driving pressure differed among the groups.

Outcomes

No significant differences were found among the different groups regarding complications, duration of ventilatory support, or length of ICU/hospital stay (Table 4). Although the in-hospital mortality rate was higher in the incompletely vaccinated group (24.2%) than in the unvaccinated and fully vaccinated groups (20.5% and 17.4%, respectively), the difference was not significant ($p = 0.813$). There were no significant differences in the study outcomes between fully vaccinated patients and partially vaccinated or

Table 1. Type of vaccine and number of doses received.

Type of vaccine [manufacturer]	Complete vaccination			Incomplete vaccination		
	1st dose (n = 23)	2nd dose (n = 23)	3rd dose (n = 11)	1st dose (n = 33)	2nd dose (n = 19)	3rd dose (n = 8)
Viral vector [AstraZeneca®]	9 (39.1)	9 (39.1)	3 (27.3)	4 (12.1)	2 (10.5)	-
Messenger RNA vaccine [Pfizer®]	8 (34.8)	8 (34.8)	-	23 (69.7)	15 (71.4)	2 (75)
Viral vector [Jansen®]	5 (21.7)	-	-	2 (6.1)	4 (21.1)	-
Messenger RNA vaccine [Moderna®]	1 (4.3)	6 (26.1)	8 (72.7)	4 (12.1)	-	8 (72.7)

Table 2. Sociodemographic, background, and clinical characteristics of patients.[a]

Characteristic	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Male sex, n (%)	204 (73.9)	161 (73.9)	24 (72.7)	19 (82.6)	0.619	185 (73.1)	0.321	43 (76.8)	0.733
Age, years	58.8 ± 13.8	57.5 ± 13.8	64.1 ± 12.8	63.5 ± 12.1	0.009	58.4 ± 1392	0.090	63.8 ± 12.4	0.003
BMI, kg/m²	30.1 ± 5.7	30.1 ± 5.4	30.2 ± 7.5	29.9 ± 6.8	0.981	30.1 ± 5.7	0.860	30.1 ± 7.1	0.969
CURB-65 score	3 (2-3)	3 (2-3)	3 (2-3.5)	3 (2-3)	0.132	3 (2-3)	0,330	3 (2-3)	0.199
SAPS II	30.3 ± 9.2	29.2 ± 8.2	35.6 ± 12.8	32.8 ± 9.1	< 0.001	30.1 ± 9.2	0.169	34.5 ± 11.4	0.002
ICU admission from, n (%)					0.509		0.612		0.609
ER	82 (29.7)	66 (30.0)	11 (33.3)	5 (21.7		112 (26.7)		16 (28.6)	
Ward	155 (56.2)	125 (56.8)	18 (54.4)	12 (52.2)		231 (55.1)		30 (53.6)	
Another hospital	39 (14.1)	29 (13.2)	4 (12.1)	6 (26.1)		76 (18.1)		10 (17.9)	
Comorbidities, n (%)									
Obesity	117 (42.4)	94 (42.7)	13 (39.4)	10 (43.5)	0.931	107 (42.3)	0.912	23 (41.1)	0.823
Smoking	18 (5.5)	15 (6.8)	3 (9.1)	-	0.390	18 (7.1)	0.378	3 (5.4)	> 0.999
Hypertension	117 (42.4)	92 (41.4)	17 (51.5)	9 (39.1)	0.517	108 (42.7)	0.741	26 (46.4)	0.534
Dyslipidemia	100 (36.2)	74 (33.6)	15 (45.5)	11 (47.8)	0.202	89 (35.2)	0.227	26 (46.4)	0.087
Diabetes mellitus	76 (27.5)	55 (25)	13 (39.4)	8 (34.8)	0.162	68 (26.9)	0.416	21 (37.5)	0.062
Chronic lung disease	51 (18.5)	40 (18.2)	6 (18.2)	5 (21.7)	0.915	46 (18.2)	0.778	11 (19.6)	0.801
Chronic heart disease	26 (9.4)	18 (8.2)	3 (9.1)	5 (21.7)	0.106	21 (8.3)	0.051	8 (14.3)	0.163
Chronic kidney disease	12 (4.3)	7 (3.2)	3 (9.1)	2 (8.7)	0.170	10 (4)	0.263	5 (8.9)	0.072
Chronic liver disease	5 (1.8)	2 (0.9)	1 (3)	2 (8.7)	0.025	3 (1.2)	0.057	3 (5.4)	0.058
Active cancer	39 (14.1)	24 (10.9)	8 (24.2)	7 (30.4)	0.008	32 (12.6)	0.029	2 (3.6)	0.184
Stroke	6 (2.2)	4 (1.8)	2 (6.1)	-	0.225	6 (2.4)	> 0.999	2 (3.6)	0.352
Autoimmune disorder	9 (3.3)	4 (1.8)	3 (9.1)	2 (8.7)	0.028	7 (2.8)	0.167	5 (8.9)	0.019
Immunosuppression	27 (9.8)	11(5)	6 (26.1)	10 (30.3)	< 0.001	21 (8.3)	0.016	16 (28.6)	< 0.001
Charlson Comorbidity Index	0 (0-2)	0 (0-1)	1 (0-2)	2 (1-2)	< 0.001	0 (0-2)	< 0.001	2 (0-2)	< 0.001
Do-not-intubate order, n (%)	12 (4.3)	10 (4.5)	1 (3)	1 (4.3)	0.924	11 (4.3)	> 0.999	2 (3.6)	> 0.999

Continue...▶

Table 2. Sociodemographic, background, and clinical characteristics of patients.[a] (Continued...)

Characteristic	All (n = 276)	Group I No vaccination (n = 220)	Group II Incomplete vaccination (n = 33)	Group III Full vaccination (n = 23)	p*	Group IV No vaccination + Incomplete vaccination (n = 253)	p**	Group V Vaccination (n = 56)	p†
Symptoms, n (%)									
Dyspnea	272 (98.6)	218 (99.1)	33 (100)	21 (91.3)	0.009	251 (99.2)	0.036	54 (96.4)	0.184
Fever	206 (74.6)	160 (72.7)	26 (78.8)	20 (87)	0.277	186 (73.5)	0.156	46 (82.1)	0.226
Dry cough	233 (84.4)	186 (84.5)	29 (87.9)	18 (78.3)	0.617	215 (85)	0.374	47 (83.9)	0.910
Expectoration	29 (10.5)	22 (10)	4 (12.1)	3 (13)	0.857	26 (10.3)	0.720	7 (12.5)	0.586
Diarrhea	29 (10.5)	25 (11.4)	2 (6.1)	2 (8.7)	0.623	27 (10.7)	>0.999	4 (7.1)	0.358
Headache	84 (30.4)	60 (27.3)	14 (42.4)	10 (43.5)	0.077	74 (29.2)	0.156	24 (42.9)	0.029
Nausea/vomiting	18 (6.5)	18 (8.2)	-	-	0.086	18 (7.1)	0.378	-	0.029
Anosmia	22 (8)	17 (7.7)	4 (12.1)	1 (4.3)	0.548	21 (8.3)	> 0.999	5 (8.9)	0.791
Ageusia	20 (7.2)	17 (7.7)	1 (3)	2 (8.7)	0.600	18 (7.1)	0.677	3 (5.4)	0.774
Chest pain	15 (5.4)	12 (5.5)	1 (3)	2 (8.7)	0.655	13 (5.1)	0.361	3 (5.4)	> 0.999
Days from symptom onset to hospital admission	7 (5-10)	7 (5-10)	6.5 (4.5-10)	7 (5-11)	0.620	7 (5-10)	0.597	7 (5-10)	0.318
Days from symptom onset to ICU admission	9 (6-11)	9 (7-11)	8.5 (6-11)	8 (5-14)	0.680	9 (7-11)	0.722	8 (6-12)	0.370
COVID-19 wave					< 0.001		< 0.001		< 0.001
3rd	108 (39.1)	107 (48.6)	1 (3)	-		108 (42.7)		1 (1.8)	
4th	11 (4)	10 (4.5)	-	1 (4.3)		10 (4)		1 (1.8)	
5th	50 (18,1)	39 (17.7)	6 (18.2)	5 (21.7)		45 (17.8)		11 (19.6)	
6th	88 (31.9)	61 (27.7)	16 (48.5)	11 (47.8)		77 (30.4)		27 (48.2)	
After the 6th wave	19 (6.9)	3 (1.4)	10 (30.3)	6 (26.1)		13 (5.1)		16 (28.6)	
First chest X-ray in the ICU, n (%)					0.544		0.705		0.244
Affected quadrants, 3-4	22 (9.1)	22 (10)	2 (6.1)	1 (4.3)		24 (9.5)		53 (94.6)	
Affected quadrants, 1-2	251 (90.9)	198 (90)	31 (93.9)	22 (95.7)		229 (90.5)		3 (5.4)	
Increased infiltrates at 48 h	214 (77.5)	170 (77.3)	23 (69.7)	21 (91.3)	0.159	193 (76.3)	0.098	44 (78.6)	0.835

CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age = 65 years; and SAPS: Simplified Acute Physiology Score. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated.
*Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

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Table 3. Treatment, analytical, and respiratory variables.[a]

Variable	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Drugs, n (%)									
Antibiotics at ICU admission	113 (40.9)	83 (37.7)	18 (37.7)	12 (52.2)	0.129	101 (39.9)	0.253	30 (53.6)	0.031
Remdesivir	11 (4.0)	9 (4.1)	9 (4.1)	-	0.299	11 (4.3)	0.608	2 (3.6)	0.859
Tocilizumab	152 (55.1)	110 (50.5)	23 (69.7)	18 (78.3)	0.188	134 (53.0)	0.020	41 (73.2)	0.002
Corticosteroids	276 (100)	220 (100)	33 (100)	23 (100)	> 0.999	253 (100)	0.999	56 (100)	> 0.999
Respiratory support at ICU admission, n (%)					0.265		0.717		0.351
HFNC	3 (1.1)	3 (1.4)	-	-		3 (1.2)		-	
CPAP	207 (75)	167 (75.9)	21 (63.6)	19 (82.6)		188 (74.3)		40 (71.4)	
BiPAP	58 (21)	45 (20.5)	9 (27.3)	4 (17.4)		54 (21.3)		13 (23.2)	
IMV	8 (2.9)	5 (2.3)	3 (9.1)	-		8 (3.2)		3 (5.34)	
Respiratory support during the ICU stay, n (%)									
HFNC	235 (85.1)	190 (86.4)	25 (75.8)	20 (87.0)	0.270	215 (85.0)	> 0.999	45 (80.4)	0.220
CPAP	237 (85.9)	189 (85.9)	27 (81.8)	21 (91.3)	0.605	216 (85.4)	0.753	48 (85.7)	0.900
BiPAP	174 (63.0)	139 (63.2)	20 (60.6)	15 (65.2)	0.936	159 (62.8)	0.822	35 (62.5)	0.875
IMV	78 (28.3)	61 (27.7)	10 (30.3)	7 (30.4)	0.927	71 (28.1)	0.809	17 (30.4)	0.646
Lymphocytes, cells × 10^9/L	560 (400-800)	500 (400-775)	500 (400-775)	600 (225-1,275)	0.856	500 (400-700)	0.833	500 (300-1,000)	0.825
D-dimer, ng/mL	894 (595-1,500)	865 (572-1,362)	600 (400-900)	767 (543-2,230)	0.010	900 (596-1,492)	0.963	1,141 (738-2,734)	0.017
Ferritin, ng/mL	911 (532-1,427)	934 (520-1,423)	1,316 (879-3,347)	833 (421-1,476)	0.706	911 (524-1,423)	0.565	781 (555-1,444)	0.359
C-reactive protein, mg/L	10.7 (5.3-19.9)	9.6 (5.3-18.1)	17.8 (9.3-26.7)	15.4 (5.1-21.6)	0.007	10.7 (5.3-20)	0.396	15 (9.8-22-5)	0.004
LDH, U/L	630 (444-838)	592 (425-805)	422 (317-550)	381 (313-512)	< 0.001	570 (401-799)	< 0.001	403 (311-533)	< 0.001
RR, breaths/min	30 ± 6	30 ± 6	29 ± 6	28 ± 5	0.155	30 ± 6	0.173	29 ± 5	0.051
PaO_2/FiO_2 at ICU admission, mmHg	115 ± 24	116 ± 24	110 ± 26	117 ± 24	0.350	115 ± 24	0.636	113 ± 22	0.398
Worst value categorized level, n (%)									
< 100 mmHg	145 (52.5)	121 (55.0)	17 (51.5)	7 (30.4)		138 (54.5)		24 (42.9)	
101-150 mmHg	130 (47.1)	99 (45.0)	16 (48.5)	15 (65.2)	0.045	115 (45.4)	0.001	31 (55.4)	
151-200 mmHg	1 (0.4)	-	-	1 (4.3)		-		1 (1.8)	0.076
PEEP/EPAP/CPAP at start NIV/IMV, mmHg									
On the day of intubation	12.1 ± 1.1	12.1 ± 1.2	11.9 ± 0.7	12.0 ± 0.8	0.654	12.1 ± 1.2	0.774	11.9 ± 0.8	0.260
Worst value	12.7 ± 1.3	12.7 ± 1.3	12.7 ± 1.1	12.4 ± 0.9	0.542	12.7 ± 1.3	0.180	12.7 ± 1.3	0.373

Continue...▶

Table 3. Treatment, analytical, and respiratory variables.[a] (Continued...)

Variable	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
Plateau pressure, cmH_2O									
On the day of intubation	24.9 ± 1.7	24.9 ± 1.6	25 ± 2.1	25.8 ± 1.3	0.343	24.9 ± 1.7	0.146	25.3 ± 1.8	0.342
Worst value during the ICU stay	27 ± 1.4	27 ± 1.3	26.8 ± 1.9	27.1 ± 1.6	0.862	26.9 ± 1.4	0.773	26.9 ± 1.7	0.836

HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; EPAP: expiratory positive airway pressure; and NIV: noninvasive ventilation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. *Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

unvaccinated patients, or between fully or partially vaccinated and unvaccinated patients.

After adjustment, the group of patients with at least one dose of vaccine and the group of unvaccinated patients showed a more balanced distribution of variables (Table 5). Although the numbers of patients with severe complications (OR = 1.49; 95% CI, 0.68-3.26), NIV failure (OR = 1.56; 95% CI, 0.68-3.59), and in-hospital mortality (OR = 1.59; 95% CI, 0.68-3.71) were higher in the unvaccinated group, none of these outcomes reached statistical significance. No significant differences were found between the two study groups regarding any of the complications analyzed in the present study (Table 6).

DISCUSSION

In this study, we found no relationship between vaccination status and outcomes in critically ill patients admitted to the ICU for ARF related to COVID-19.

Since the onset of the COVID-19 pandemic, an immense effort has been made to develop strategies to contain infection with SARS-CoV-2. The development of vaccines and their availability to the population was one of the priorities. Vaccines have shown high efficacy in preventing severe disease, resulting in lower rates of hospitalization, ICU admission, need for mechanical ventilation, and, ultimately, mortality.[7-11] These findings have been observed in different geographic settings.[20-24] However, in patients admitted to the ICU for critical COVID-19, the outcomes and their relationship with vaccination status are controversial.

In a small study conducted in 2021, Morales et al. showed no significant differences in length of stay or mortality between fully vaccinated, partially vaccinated, and unvaccinated patients.[13] Grapsa et al. analyzed patients with ARDS caused by COVID-19 and the need for invasive mechanical ventilation, finding lower mortality in patients with complete vaccination than in controls who were either unvaccinated or partially vaccinated.[14] Graselli et al. showed that although vaccination decreased the risk of ICU admission, vaccination status was not related to ICU or in-hospital mortality in patients admitted to the ICU.[15] Finally, in a multicenter study of patients admitted to ICU, Otto et al. showed that vaccinated patients had fewer days of invasive mechanical ventilation, ICU stay, and hospital stay.[16] Although crude mortality was higher in vaccinated patients, adjusted mortality by multivariate analysis showed no relationship between vaccination status and ICU or in-hospital mortality.

As in previous studies, we found that vaccinated patients were older and had more comorbidities,[13-16] probably because older individuals with comorbidities constitute the main target of vaccination campaigns. In the unvaccinated group, we found a higher proportion of patients with severe ARF (PaO_2/FiO_2 < 100 mmHg) at ICU admission, as well as increased levels of LDH and D-dimer, which are parameters related to worse clinical prognosis.[25] However, C-reactive protein

Table 4. Patient outcomes.[a]

Outcome	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
ARDS, n (%)	259 (93.6)	206 (93.6)	32 (97.0)	21 (91.3)		238 (94.1)		53 (94.6)	
Grade, n (%)					0.660		0.641		> 0.999
Moderate	96 (37.1)	76 (36.9)	12 (37.5)	8 (38.1)	0.993	88 (37.0)	0.919	20 (37.7)	0.910
Severe	163 (62.9)	130 (63.1)	20 (62.5)	13 (61.9)		150 (63.0)		33 (62.3)	
SOFA score at ICU admission									
Worst value during the ICU stay	3.6 ± 1.2	3.6 ± 1.1	4.1 ± 1.9	3.6 ± 0.9	0.058	3.7 ± 1.2	0.745	3.9 ± 1.6	0.157
	6.1 ± 3.7	5.9 ± 3.7	6.5 ± 3.7	6.2 ± 3.5	0.705	6.1 ± 3.7	0.816	6.4 ± 3.6	0.438
Hyperglycemia, n (%)	99 (35.9)	84 (38.2)	9 (27.3)	6 (26.1)	0.282	93 (36.8)	0.307	15 (26.8)	0.112
Severe bleeding, n (%)	10 (3.6)	10 (4.5)	-	-	0.267	10 (4.0)	> 0.999	-	0.221
Acute kidney injury, n (%)	67 (24.3)	50 (22.7)	10 (30.3)	7 (30.4)	0.493	60 (23.7)	0.472	17 (30.4)	0.234
Agitation/hyperactive delirium, n (%)	64 (23.2)	49 (22.3)	7 (21.2)	8 (34.8)	0.296	56 (22.1)	0.169	15 (26.8)	0.523
Weakness acquired in the ICU, n (%)	56 (20.3)	43 (19.5)	7 (21.2)	6 (26.1)	0.752	50 (19.8)	0.470	12 (23.2)	0.542
Thromboembolic disease, n (%)	21 (7.6)	16 (7.3)	3 (9.1)	2 (8.7)	0.915	19 (7.5)	0.690	5 (8.9)	0.777
Atrial fibrillation, n (%)	22 (8.0)	20 (9.1)	-	2 (8.7)	0.197	20 (7.9)	0.703	2 (3.6)	0.268
Stroke, n (%)	4 (1.4)	4 (1.8)	-	-	0.597	4 (1.6)	> 0.999	-	0.586
Barotrauma, n (%)	46 (16.7)	39 (17.7)	4 (12.1)	3 (13.0)	0.642	43 (17.0)	0.776	7 (12.5)	0.349
Nosocomial infection, n (%)	102 (37.0)	82 (37.3)	9 (27.3)	11 (47.8)	0.286	91 (36.0)	0.259	20 (35.7)	0.781
First-line NIV failure	79 (29.5)	64 (29.8)	7 (23.3)	8 (34.8)	0.649	71 (29.0)	0.559	15 (28.3)	0.849
First-line NIV failure with DNI order	70 (27,3)	56 (27,3)	7 (24,1)	7 (31,8)	0.830	63 (26.0)	0.622	14 (27,5)	0.985
Post-extubation NIV failure	5 (17.2)	4 (16.7)	1 (50.0)	-	0.344	5 (10.2)	> 0.999	1 (20.0)	> 0.999
NIV duration, days	6 (3-10)	5 (3-10)	7 (3-11)	6 (5-15)	0.865	5.5 (3-10)	0.852	6 (4-12)	0.813
IMV duration, days	13 (6-29)	13 (6-28)	7 (2-19)	35 (10-56)	0.051	13 (6-25)	0.055	11 (4-35)	0.811
Tracheotomy, n (%)	31 (11.2)	24 (10.9)	2 (6.1)	5 (21.7)	0.178	26 (10.3)	0.156	7 (12.5)	0.736
ECMO, n (%)	4 (1.4)	4 (1.4)	-	-	0.597	4 (1.6)	> 0.999	-	0.586
ICU stay, days	27 (14-43)	27 (15-45)	14 (6-31)	43 (26-87)	0.798	24 (13-43)	0.522	10 (6.0-16.5)	0.875
Hospital stay, days	32 (18-51)	39 (19-51)	17 (6-31)	50 (26-129)	0.583	30 (17-50)	0.300	18 (11-26)	0.628
ICU mortality	55 (19.9)	43 (19.5)	8 (24.2)	4 (17.4)	0.780	51 (20.2)	> 0.999	12 (21.4)	0.753
ICU mortality with DNI order	46 (17,4)	35 (16.7)	8 (25.0)	3 (13,6)	0.454	43 (17.8)	0.625	11 (20.3)	0.522

Continue...▶

Table 4. Patient outcomes.[a] (Continued...)

Outcome	All	Group I	Group II	Group III	p*	Group IV	p**	Group V	p†
		No vaccination	Incomplete vaccination	Full vaccination		No vaccination + Incomplete vaccination		Vaccination	
	(n = 276)	(n = 220)	(n = 33)	(n = 23)		(n = 253)		(n = 56)	
In-hospital mortality	57 (20.7)	45 (20.5)	8 (24.2)	4 (17.4)	0.813	53 (19.3)	0.795	12 (21.4)	0.932
In-hospital mortality with DNI order	48 (18.2)	37 (17.6)	8 (25.0)	3 (13.6)	0.509	45 (18.6)	0.564	11 (20.4)	0.640

NIV: noninvasive ventilation; DNI: do-not-intubate; IMV: invasive mechanical ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. *Comparison between Group I, Group II, and Group III. **Comparison between Group III and Group IV. †Comparison between Group I and Group V. NOTE: Group I (no vaccination): patients who did not receive any COVID-19 vaccine; Group II (incomplete vaccination): patients who did not receive all recommended doses of COVID-19 vaccine, including booster doses (when approved by health authorities), to ensure proper immunization or who developed COVID-19 less than 14 days or more than 5 months after the last dose received; Group III (full vaccination): patients who received the required doses, in accordance with the type of vaccine used, including booster doses (when approved by health authorities), to ensure proper immunization, with more than 14 days and less than 5 months between the last dose of vaccine and the development of COVID-19; Group IV (no vaccination + incomplete vaccination, i.e., Group I and II patients); and Group V (vaccination, i.e., Group II and III patients).

levels—a parameter related to the inflammatory process—were higher in vaccinated patients, especially fully vaccinated patients. Nevertheless, the main results regarding complications of COVID-19, length of ICU/hospital stay, and mortality were unrelated to vaccination status. We accounted for variations in the prevalence of different SARS-CoV-2 variants during the study period, which could have modified the vaccination results by adjusting for the variable "wave of the COVID-19 pandemic" (grouping together patients admitted during waves 3 and 4, and those admitted during waves 5, 6, and later) in the paired analysis.

Although previous studies have used different definitions of partially vaccinated patients, we have used the definition suggested by the U.S. Centers for Disease Control and Prevention, a definition that was also used in the aforementioned multicenter study in Greece.[14] This definition takes into account whether or not the booster dose has been received, as recommended by health authorities. In order to assess the potential impact of vaccination on clinical outcomes in critically ill patients, we made comparisons by dividing patients into three groups on the basis of their vaccination status. These comparisons were aimed at evaluating any differences or associations between vaccination status and clinical outcomes. Given the uncertainty about the role of incomplete vaccination in patient outcomes, we performed further analyses by grouping partially vaccinated patients and unvaccinated patients, and by comparing unvaccinated patients with those who had received at least one dose of vaccine. None of these analyses, including a propensity score-matched analysis comparing unvaccinated patients and patients who had received at least one dose of vaccine, showed a better prognosis in fully vaccinated or partially vaccinated patients. Multiple factors may contribute to the fact that vaccination does not protect against critical COVID-19, including age, vaccine type, virus variant, and immunosuppression.[26] In addition, other, unknown, factors may contribute to the lack of vaccine efficacy in vaccinated patients presenting with severe COVID-19. Despite these findings, in the absence of a statistically significant difference, it is important to note that the proportions of patients with severe complications, NIV failure, and in-hospital mortality were higher in unvaccinated patients than in those who had received at least one dose of vaccine in the propensity-matched sample. The presence of an OR of 1.93 for in-hospital mortality is relevant even in the absence of statistical significance and could provide further evidence for systematic vaccination against COVID-19, not only because it might reduce the risk of infection and severe disease but also because outcomes might be worse in unvaccinated patients who are critically ill.

Our study has several limitations. First, although the sample size was large (276 critically ill patients), the groups of patients with complete and incomplete

Table 5. Comparison of patient sociodemographic, clinical, and analytical characteristics matched by propensity score analysis.[a]

Variable	Vaccination (n = 52)	No vaccination (n = 52)	p	SMD, %
Male sex, n (%)	39 (75)	39 (75)	> 0.999	-
Age, years	63.1 ± 12.6	61.9 ± 13.7	0.551	8.3
Comorbidities, n (%)				
Obesity	22 (43.3)	20 (38.5)	0.845	5.4
Current smoking	3 (5.8)	2 (3.8)	> 0.999	6.2
Hypertension	24 (46.2)	22 (42.3)	0.832	5.9
Dyslipidemia	23 (44.2)	20 (38.5)	0.690	8.3
Diabetes mellitus	18 (34.6)	16 (30.8)	0.804	6.9
Chronic lung disease	11 (21.2)	11 (21.2)	> 0,999	-
Chronic heart disease	7 (13.5)	5 (9.6)	0.727	9.8
Chronic kidney disease	5 (9.6)	4 (7.7)	> 0.999	4.6
Chronic liver disease	3 (5.8)	2 (3,8)	> 0.999	6.2
Active cancer	2 (3.8)	3 (5.8)	> 0.999	6.5
Stroke	2 (3.8)	2 (3.8)	> 0.999	8.0
Autoimmune disorder	1 (1.9)	2 (3.8)	> 0.999	8.0
Immunosuppression	10 (19.2)	10 (19.2)	> 0.999	-
Charlson Comorbidity Index	2 (1-3)	2 (1-3)	0.963	6.3
COVID-19 wave, n (%)			> 0.999	3.3
3rd to 5th	13 (25.0)	14 (26.9)		
6th and later	39 (75.0)	38 (73.1)		
ICU admission from the ER, n (%)	12 (23.1)	12 (23.1)	> 0.999	-
CURB-65	3 (2-3)	3 (2-3)	0.204	17.1
SAPS II	33.4 ± 10.1	32.2 ± 7.2	0.328	13.7
Do-not-intubate order, n (%)	2 (3.8)	3 (5.8)	> 0.999	6.2
Days from symptom onset to hospital admission	7 (5-9)	7 (5-10)	0.337	11.1
Days from symptom onset to ICU admission	8 (6-12)	8 (7-12)	0.795	2.0
3-4 quadrants affected on the first chest X-ray in the ICU, n (%)	49 (94.2)	47 (90.4)	0.727	9.8
Increased infiltrates at 48 h, n (%)	42 (80.8)	35 (67.3)	0.167	22.6
Respiratory support at ICU admission, n (%)				
CPAP	37 (71.2)	39 (75.0)	0.851	5.2
BiPAP	12 (23.1)	13 (25.0)	> 0.999	2.7
Other (HFNC/IMV)	3 (5.8)	1 (4.5)	0.625	13.9
Drugs, n (%)				
Antibiotics at ICU admission	27 (51.9)	17 (32.7)	0.076	28.0
Remdesivir	2 (3,8)	2 (3.8)	> 0.999	-
Tocilizumab	36 (69.2)	33 (63.5)	0.648	9.5
Corticosteroids	52 (100)	52 (100)	> 0.999	-
D-dimer, ng/mL	1,281 (756-2,884)	1,068 (771-2,103)	0.278	2.3
C-reactive protein, mg/L	12.8 (5.2-21.3)	15.0 (9.5-20.8)	0.006	31.6
LDH, U/L	399 (302-535)	531 (393-783)	0.003	44.8
RR, breaths/min	29 ± 5	30 ± 7	0.557	8.2
PaO_2/FiO_2 at ICU admission, mmHg	112 ± 21	114 ± 17	0.554	8.3

SMD: standardized mean difference; CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age = 65 years; SAPS: Simplified Acute Physiology Score; HFNC: high-flow nasal cannula; and IMV: invasive mechanical ventilation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated.

vaccination were relatively small. This may have impacted the statistical significance of the differences among groups. Second, because this was a single-center study with a working protocol based mainly on the treatment of ARF with NIV, the results may be more closely related to patient management than to vaccination status. Finally, we analyzed all patients admitted since vaccination began, regardless of the predominant variant. The Delta variant predominated during the first few months after initiation of vaccination, with the Omicron variant predominating from September of 2021 onward. However, correlation studies conducted in Europe showed that, although vaccination did not significantly improve the infection rate in the first four months of 2022, it had an impact on health care systems, hospitalizations, ICU admissions, and mortality.[27] This benefit diminished in the last month of 2022, a finding that is consistent with previous observations and indicates that, although a booster dose temporarily restores antibody levels

Table 6. Comparison of patient outcomes matched by propensity score analysis.[a]

Variable	Vaccination (n = 52)	No vaccination (n = 52)	p	SMD, %
Respiratory support during the ICU stay, n (%)				
HFNC	41 (78.8)	47 (90.4)	0.109	0.27
CPAP	44 (84.6)	45 (86.5)	> 0.999	3.5
BiPAP	33 (63.5)	36 (69.2)	0.678	8.6
IMV	16 (30.8)	16 (30.8)	-	-
SOFA score at ICU admission	4.0 ± 1.6	3.9 ± 0.9	0.659	6.2
Worst value during the ICU stay	6.4 ± 3.5	6.4 ± 3.9	0.878	2.1
Patients with complications, n (%)	28 (53.8)	33 (63,5)	0.487	12.0
Hyperglycemia, n (%)	14 (26.9)	15 (28.8)	> 0.999	3.0
Severe bleeding, n (%)	-	3 (5.8)	-	24.5
Acute kidney injury, n (%)	15 (28.8)	13 (25.0)	0.815	6.5
Agitation/hyperactive delirium, n (%)	15 (28.8)	13 (25.0)	0.804	6.9
Weakness acquired in the ICU, n (%)	12 (23.1)	8 (15.4)	0.424	14.7
Thromboembolic disease, n (%)	5 (9.6)	3 (5.8)	0.727	9.8
Atrial fibrillation, n (%)	2 (3.8)	5 (9.6)	0.453	15.8
Barotrauma, n (%)	6 (11.5)	4 (7.7)	0.754	8.7
Nosocomial infection, n (%)	18 (34.6)	20 (38.5)	0.815	6.5
First-line NIV failure[b], n (%)	14 (28.6)	19 (36.5)	0.664	9.3
NIV duration, days	5 (3-7)	4 (3-7)	0.824	1.5
IMV duration, days	14 (8-21)	13 (9-22)	0.927	5.2
Tracheotomy, n (%)	6 (11.5)	3 (5.8)	0.508	13.9
ECMO, n (%)	-	1 (1.9)	-	13.9
ICU stay, days	10.5 (6-19.5)	10 (6-16.5)	0.912	7.8
Hospital stay, days	19 (12-26.5)	18 (11-26)	0.725	10.7
ICU mortality, n (%)	12 (23.1)	16 (30.8)	0.503	12.4
In-hospital mortality, n (%)	13 (25.0)	18 (34.6)	0.405	14.5

SMD: standardized mean difference; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Data expressed as mean ± SD or median (interquartile range), except where otherwise indicated. [b]In 101 patients receiving first-line NIV or after failure of HFNC (49 patients in the vaccination group and 52 patients in the no vaccination group).

and boosts cell-mediated immunity, protection from different outcomes of Omicron infection begins to wane 3-4 months after administration.[27]

It is well demonstrated that vaccines prevent hospitalization, severe disease, and death from COVID-19.[28] What is not as clear is how vaccinated or partially vaccinated patients fare in comparison with unvaccinated patients once COVID-19–related ARF is established. This study failed to show a significant improvement in outcomes in critically ill COVID-19 patients vaccinated against SARS-CoV-2. However, the CIs were wide and the mortality point estimates favored patients who received at least one dose of COVID-19 vaccine. Further, larger, studies are needed in order to determine the connection between vaccination status and prognosis of critical COVID-19, as well as to match patient-related factors, vaccine type, and virus variant with their effects on these patients.

AUTHOR CONTRIBUTIONS

Pedro Nogueira Costa planned the study, interpreted the data, and wrote the article. The remaining authors participated in data collection and interpretation, having reviewed the final draft of the article.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Brainard J, Jones NR, Lake IR, Hooper L, Hunter PR. Community use of face masks and similar barriers to prevent respiratory illness such as COVID-19: a rapid scoping review. Euro Surveill. 2020;25(49):2000725. https://doi.org/10.2807/1560-7917.ES.2020.25.49.2000725
2. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect Dis. 2021;21(2):e26-e35. https://doi.org/10.1016/S1473-3099(20)30773-8
3. Korang SK, von Rohden E, Veroniki AA, Ong G, Ngalamika O, Siddiqui F, et al. Vaccines to prevent COVID-19: A living systematic review with Trial Sequential Analysis and network meta-analysis of randomized clinical trials. PLoS One. 2022;17(1):e0260733. https://doi.org/10.1371/journal.pone.0260733
4. Wada N, Li Y, Hino T, Gagne S, Valtchinov VI, Gay E, et al. COVID-19 Vaccination reduced pneumonia severity. Eur J Radiol Open.

2022;9:100456. https://doi.org/10.1016/j.ejro.2022.100456

5. Singhal J, Goel C, Gupta V, Sachdeva M, Sanjappa S, Koushal V, et al. Comparison of Imaging Severity Between Vaccinated and Unvaccinated COVID-19 Patients: Perspective of an Indian District. Cureus. 2022;14(10):e30724. https://doi.org/10.7759/cureus.30724
6. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021;398(10309):1407-1416. https://doi.org/10.1016/S0140-6736(21)02183-8
7. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association Between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA. 2021;326(20):2043-2054. https://doi.org/10.1001/jama.2021.19499
8. He X, Su J, Ma Y, Zhang W, Tang S. A comprehensive analysis of the efficacy and effectiveness of COVID-19 vaccines. Front Immunol. 2022;13:945930. https://doi.org/10.3389/fimmu.2022.945930
9. Whittaker R, Bråthen Kristofferson A, Valcarcel Salamanca B, Seppälä E, Golestani K, Kvåle R, et al. Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients. Clin Microbiol Infect. 2022;28(6):871-878. https://doi.org/10.1016/j.cmi.2022.01.033
10. Rotshild V, Hirsh-Raccah B, Miskin I, Muszkat M, Matok I. Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. Sci Rep. 2021;11(1):22777. https://doi.org/10.1038/s41598-021-02321-z
11. Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H, et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev. 2022;12(12):CD015477. https://doi.org/10.1002/14651858.CD015477
12. Federico M. How Do Anti-SARS-CoV-2 mRNA Vaccines Protect from Severe Disease?. Int J Mol Sci. 2022;23(18):10374. https://doi.org/10.3390/ijms231810374
13. Morales Varas G, Sánchez Casado M, Padilla Peinado R, Morán Gallego F, Buj Vicente M, Rodríguez Villamizar A. Effects of vaccination against COVID-19 on the evolution of critically ill patients. Med Intensiva (Engl Ed). 2022;46(10):588-590. https://doi.org/10.1016/j.medin.2021.12.009
14. Grapsa E, Adamos G, Andrianopoulos I, Tsolaki V, Giannakoulis VG, Karavidas N, et al. Association Between Vaccination Status and Mortality Among Intubated Patients With COVID-19-Related Acute Respiratory Distress Syndrome. JAMA Netw Open. 2022;5(10):e2235219. https://doi.org/10.1001/jamanetworkopen.2022.35219
15. Grasselli G, Zanella A, Carlesso E, Florio G, Canakoglu A, Bellani G, et al. Association of COVID-19 Vaccinations With Intensive Care Unit Admissions and Outcome of Critically Ill Patients With COVID-19 Pneumonia in Lombardy, Italy. JAMA Netw Open. 2022;5(10):e2238871. https://doi.org/10.1001/jamanetworkopen.2022.38871
16. Otto M, Burrell AJC, Neto AS, Alliegro PV, Trapani T, Cheng A, et al. Clinical characteristics and outcomes of critically ill patients with one, two and three doses of vaccination against COVID-19 in Australia. Intern Med J. 2023;53(3):330-338. https://doi.org/10.1111/imj.15884
17. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study [published correction appears in JAMA 1994 May 4;271(17):1321]. JAMA. 1993;270(24):2957-2963. https://doi.org/10.1001/jama.1993.03510240069035
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-710. https://doi.org/10.1007/BF01709751
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383. https://doi.org/10.1016/0021-9681(87)90171-8
20. Johnson S, Mielke N, Mathew T, Maine GN, Chen NW, Bahl A. Predictors of hospitalization and severe disease due to breakthrough SARS-CoV-2 infection in fully vaccinated individuals. J Am Coll Emerg Physicians Open. 2022;3(4):e12793. https://doi.org/10.1002/emp2.12793
21. Semenzato L, Botton J, Baricault B, Deloumeaux J, Joachim C, Sylvestre E, et al. Vaccine effectiveness against severe COVID-19 outcomes within the French overseas territories: A cohort study of 2-doses vaccinated individuals matched to unvaccinated ones followed up until September 2021 and based on the National Health Data System. PLoS One. 2022;17(9):e0274309. https://doi.org/10.1371/journal.pone.0274309
22. Baum U, Poukka E, Leino T, Kilpi T, Nohynek H, Palmu AA. High vaccine effectiveness against severe COVID-19 in the elderly in Finland before and after the emergence of Omicron. BMC Infect Dis. 2022;22(1):816. https://doi.org/10.1186/s12879-022-07814-4
23. Gram MA, Emborg HD, Schelde AB, Friis NU, Nielsen KF, Moustsen-Helms IR, et al. Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the Alpha, Delta, or Omicron SARS-CoV-2 variant: A nationwide Danish cohort study. PLoS Med. 2022;19(9):e1003992. https://doi.org/10.1371/journal.pmed.1003992
24. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, AlMukdad S, Yassine HM, Al-Khatib HA, et al. Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. N Engl J Med. 2022;386(19):1804-1816. https://doi.org/10.1056/NEJMoa2200797
25. Keykavousi K, Nourbakhsh F, Abdollahpour N, Fazeli F, Sedaghat A, Soheili V, et al. A Review of Routine Laboratory Biomarkers for the Detection of Severe COVID-19 Disease. Int J Anal Chem. 2022;2022:9006487. https://doi.org/10.1155/2022/9006487
26. Petráš M, Máčalík R, Janovská D, Čelko AM, Dáňová J, Selinger E, et al. Risk factors affecting COVID-19 vaccine effectiveness identified from 290 cross-country observational studies until February 2022: a meta-analysis and meta-regression. BMC Med. 2022;20(1):461. https://doi.org/10.1186/s12916-022-02663-z
27. Rzymski P, Kasianchuk N, Sikora D, Poniedziałek B. COVID-19 vaccinations and rates of infections, hospitalizations, ICU admissions, and deaths in Europe during SARS-CoV-2 Omicron wave in the first quarter of 2022. J Med Virol. 2023;95(1):e28131. https://doi.org/10.1002/jmv.28131
28. Tenforde MW, Self WH, Gaglani M, Ginde AA, Douin DJ, Talbot HK, et al. Effectiveness of mRNA Vaccination in Preventing COVID-19-Associated Invasive Mechanical Ventilation and Death - United States, March 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(12):459-465. https://doi.org/10.15585/mmwr.mm7112e1

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https://dx.doi.org/10.36416/1806-3756/e20230305

ORIGINAL ARTICLE

Persistence of symptoms and lung function in mild cases of COVID-19 six months after infection: a cross-sectional study

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ABSTRACT

Objectives: To describe persistent symptoms and lung function in mild cases of COVID-19 six months after infection. **Methods:** Data collection was performed through a semi-structured questionnaire containing information on the participants' demographic and anthropometric data, the disease in the acute phase, and persistent symptoms six months after COVID-19 using spirometry and manovacuometry. **Results:** A total of 136 participants were evaluated, of whom 64% were male, with a mean age of 38.17 ± 14.08 years and a body mass index (BMI) of 29.71 ± 17.48 kg/m^2. The main persistent symptoms reported were dyspnea on exertion (39.7%), memory loss (38.2%), and anxiety (48.5%). Considering lung function, the participants reached 88.87 ± 17.20% of the predicted forced vital capacity (FVC), 86.03 ± 22.01% of the forced expiratory volume in one second (FEV1), and 62.71 ± 25.04% of peak expiratory flow (PEF). Upon manovacuometry, 97.41 ± 34.67% of the predicted inspiratory force (Pimax) and 66.86 ± 22.97% of the predicted expiratory force (Pemax) were observed. **Conclusions:** Six months after COVID-19 infection, a reduction in PEF and MEP was observed. Among the most commonly reported persistent symptoms were fatigue, tiredness with the slightest exertion, anxiety and depression, memory loss, and deficits in concentration.

Keywords: Post-acute COVID-19 Syndrome, Respiratory Function Tests, Dyspnea.

INTRODUCTION

The first cases of the novel coronavirus disease were reported in 2019 (COVID-19) in the city of Wuhan, China. This virus belongs to a family of viruses that cause infections in various systems of the human body. Despite its predilection for the respiratory tract, it also affects the liver, central nervous system, and enteric system in humans. Known for its previously caused outbreaks, the one that began in 2019 was triggered by a strain known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has high transmissibility, leading to the widespread proliferation of the virus and the emergence of a global pandemic.[1,2]

Among COVID-19 cases, 80% may be asymptomatic or have mild symptoms. Approximately 20% of those infected will require hospitalization, 5% of whom may progress to the need for invasive mechanical ventilation. The disease affects several systems of the human body, leading to complications such as kidney failure, pneumonia, acute respiratory distress syndrome (ARDS), coagulopathies, thromboembolic events, bacterial infections, sepsis, and death.[3]

According to the literature, it is already known that even after recovery, some symptoms can persist, including dyspnea, weakness, and sleep changes, as well as physiological, cardiac, and radiological alterations. These symptoms can persist for months. Post-COVID syndrome is defined as the persistence of symptoms 12 weeks after infection, whether they developed during or after the infection period, and that are not explained by any other diagnosis.[4-6]

Patients who have developed the severe form of the disease are discharged with some degree of physical or emotional impairment, but symptom persistence has also affected those who had the mild form of COVID-19. A survey carried out in the UK with around 3,700 participants found that 92% of those interviewed did not require hospitalization, and, among these, 93% still had persistent symptoms. Among the participants were individuals who had been experiencing symptoms for more than 7 months post-infection.[7,8]

Considering the natural course of the disease, it is expected that some symptoms will persist after recovery. However, it is crucial to identify the most prevalent symptoms reported by the majority of COVID-19 cases, particularly individuals who have had mild cases. Given the virus's preference for the respiratory system, it is also important to investigate potential changes in lung function caused by COVID-19. Therefore, the aim of the present study was to describe persistent symptoms and lung function in individuals with mild cases of COVID-19 six months after infection.

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METHODS

This cross-sectional study was carried out at the Cardiorespiratory Physiotherapy Laboratory of the Federal University of Ceará, in the city of Fortaleza (CE), Brazil. Data collection took place from March to June 2022.

The study included individuals aged 18 and above with a confirmed diagnosis of COVID-19 six months prior, classified as mild according to the recommendations of the Ministry of Health (2020), i.e., those who did not require hospitalization and supplemental oxygen.[6] Participants with any communication or comprehension disorders that hindered their ability to conduct the interview and/or perform respiratory function tests, as well as those with disease reinfection during the data collection period, individuals engaged in regular physical activity, and those who had undergone post-COVID-19 rehabilitation, were excluded from the study (Figure 1).

Initially, the participants completed a semi-structured questionnaire that included information on age, sex, height, weight, drinking and/or smoking habits, the number of vaccinations, COVID-19 recurrence, and any previous lung or heart disease. The second part of the questionnaire focused on the symptoms that persisted after the disease, with the participants' self-reporting regarding the musculoskeletal, neurological, dermatological, cardiovascular, and respiratory systems, as well as their psycho-emotional condition. In addition, the participants provided information on the need for assistance with activities of daily living and the disruption of social, occupational, and leisure activities following COVID-19 infection.

Subsequently, a respiratory assessment was conducted, comprising an evaluation of respiratory muscle strength by manovacuometry and pulmonary function by spirometry. Both inspiratory and expiratory respiratory muscle strength were measured. In order to determine the value obtained for each individual, each maneuver was performed three times, with the highest result considered the best. If a learning effect was observed, the procedure could be repeated up to five times. The parameters for comparison were based on values suggested for the Brazilian population.[9,10]

Data on forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) were collected via spirometry. The test was carried out using the FVC maneuver, which was performed three times, with the best result being considered. Similar to manovacuometry, the maneuver could be repeated up to five times if the evaluator noticed a learning effect. The predicted values for each participant were determined using Pereira's formula (2007), which is validated for the Brazilian population.[11]

All data were structured and analyzed using IBM SPSS Statistics software, version 20. Descriptive analysis was performed on the aforementioned data, and the results were expressed as means and standard deviation, frequencies, and percentages.[12]

This study was approved by the Research Ethics Committee involving human beings of the Federal University of Ceará (CAAE No. 64780022.1.0000.5054), in accordance with Resolution 466/12 of the National Health Council (CNS).

RESULTS

Demographic, anthropometric, and clinical data related to the period of COVID-19 infection

The analysis included 135 individuals who had confirmed COVID-19 six months prior to the evaluation period. The sample had a mean age of 38.10 ± 14.12 years, a BMI of 29.72 ± 17.54 kg/m^2, and 63.7% were men. Among the participants, 29.6% had experienced COVID-19 more than once. Of those included in the study, 11% had a history of previous lung disease, including asthma, and 14% had a history of previous heart disease. In addition to the data characterizing the sample, Table 1 shows the symptoms reported during the acute COVID-19 infection, with the most prevalent being dyspnea, fever, cough, and body pain.

Respiratory muscle strength and lung function six months after COVID-19 infection

With regard to the maximum inspiratory pressure (MIP), the participants obtained a mean of 84.14 ± 49.37 cm/H_2O, representing 97.41 ± 34.67% of the predicted value. The mean maximum expiratory pressure (MEP) was 89.44 ± 29.49 cm/H_2O, and 66.86 ± 22.97% of the predicted level was achieved. The spirometry results showed a mean FVC of 3.40 ± 0.95 L, corresponding to 88.87 ± 17.20% of the predicted

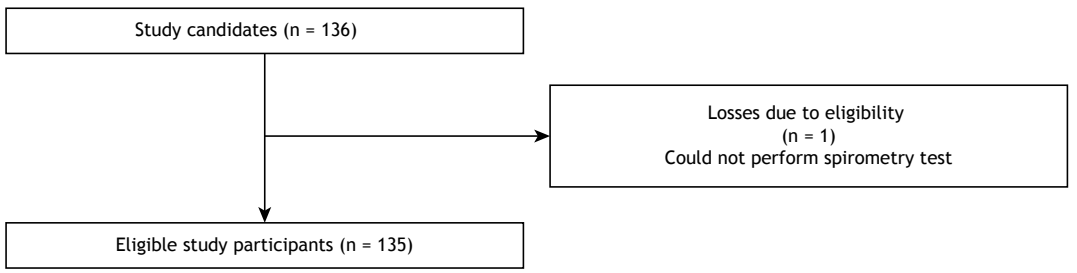

Figure 1. Flowchart of study sample selection.

Table 1. Demographic, anthropometric, and clinical data related to the period of COVID-19 infection. Fortaleza (CE), 2022.

Variables	N = 135
Age, years (mean ± SD)	38.10 ± 14.12
Body Mass Index (weight/height²) (BMI)	29.72 ± 17.54
Male sex, n (%)	86 (63.7)
Smoking, n (%)	10 (7.4)
Alcoholism, n (%)	55 (40.7)
Previous lung disease, n (%)	15 (11)
Previous heart disease, n (%)	19 (14)
COVID-19 more than once, n (%)	40 (29.6)
Symptoms related to the acute period of COVID-19 infection	
Fever, n (%)	79 (58.5)
Dyspnea, n (%)	100 (74.1)
Fatigue, n (%)	40 (29.6)
Sore throat, n (%)	38 (28.1)
Runny nose, n (%)	36 (26.7)
Cough, n (%)	74 (54.8)
Body pain, n (%)	72 (53.3)

value, and a mean expired volume of 2.70 ± 0.92 L, reaching 86.03 ± 22.01% of the predicted value. The mean PEF was 4.57 ± 2.25 L/min, corresponding to 62.71 ± 25.04% of the expected value. Table 2 shows the results of the respiratory assessment.

Persistent symptoms six months after COVID-19 infection

In the self-report, the most frequently persistent symptoms were respiratory, observed in 80% of the sample, with 40% of the participants reporting tiredness upon slight exertion. The second-highest prevalence of persistent symptoms was psychological, reported by 75.6% of the assessed participants, with anxiety present in 48.1% of the reports. Memory loss was described by 37.8% of the participants, contributing to the 74.8% who persisted with neurological symptoms, making it the third most affected system.

The persistence of symptoms in the integumentary system was described by 57.8% of the participants in our study, with hair loss being the most common symptom, present in 32.6% of the reports from this group. Regarding the musculoskeletal system, 53.3% of the participants reported persistent symptoms, with muscle fatigue/weakness mentioned in 23.7% of the reports, followed by myoarticular pain in 23%. Palpitation was reported by 22.2% of the participants, contributing to the 44.4% who reported persistent cardiovascular symptoms.

Among the study participants, 20% required assistance with instrumental activities of daily living after the acute phase of the disease, and 34.8% discontinued social, occupational, and/or leisure activities due to the persistent symptoms. The aforementioned data is shown in Table 3.

DISCUSSION

Our findings from the respiratory assessment indicate that the parameters of FVC, FEV1, and MIP were within the normal range, while MEP and PEF were lower than expected six months after COVID-19. The most commonly reported persistent symptoms following infection included tiredness upon slight exertion, anxiety, and memory loss. The participants also reported the need for assistance with basic and instrumental activities of daily living after recovering from the disease, and the absence of social, occupational, and/or leisure activities due to persistent symptoms.

The persistence of symptoms for more than 12 weeks is characterized as post-COVID-19 syndrome. A cohort study was conducted with participants who were not hospitalized due to COVID-19, and a follow-up was carried out one year after infection to assess the persistence of symptoms. Among the 336 participants, 156 (47%) reported symptom persistence. The cohort summarized the symptoms of the acute phase of COVID-19 infection, and the results were similar to those found herein, with the most prevalent symptoms in that phase being fatigue, fever, body pain, cough, runny nose, and dyspnea.[12]

In analyzing respiratory muscle strength, it was observed that the MEP reached a predicted level, implying a functional diagnosis of expiratory muscle weakness. This reduction may be attributed to the loss of muscle strength caused by the inflammatory process of COVID-19 and the persistence of symptoms, particularly muscle fatigue, a symptom reported in our sample. This finding may also explain the reduction in PEF, which is influenced by expiratory muscle strength.[13-15]

As for the MIP, our sample performed better than expected. Another finding that may be related to the above is the overweight status according to the BMI. Previous studies have reported a positive relationship between body weight and MIP, relating the isometric length of different muscle groups to weight – a phenomenon known as the 'muscularity effect'. In this

Table 2. Respiratory muscle strength and lung function of study participants six months after COVID-19 infection. Fortaleza (CE), 2022.

Respiratory muscle strength	Achieved (mean ± SD)	Expected % (mean ± SD)
MIP (cm/H_2O)	84.14 ± 49.37	97.41 ± 34.67
MEP (cm/H_2O)	89.44 ± 29.49	66.86 ± 22.97
Lung Function	**Achieved (mean ± SD)**	**Expected % (mean ± SD)**
FVC (L)	3.40 ± 0.95	88.87 ± 17.20
FEV1 (L)	2.70 ± 0.92	86.03 ± 22.01
PEF (L/min)	4.57 ± 2.25	62.71 ± 25.04

SD: Standard Deviation; MIP: Maximum Inspiratory Pressure; MEP: Maximum Expiratory Pressure; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the first second; PEF: Peak Expiratory Flow.

Table 3. Persistent COVID-19 symptoms six months after infection. Fortaleza (CE), 2022.

Persistent symptoms after the COVID-19 infection period	
Cardiovascular	60 (44.4)
Palpitation	30 (22.2)
Chest pain	2 (1.5)
SAH	5 (3.7)
Palpitation and SAH	23 (17.0)
Respiratory	108 (80)
Minor fatigue	54 (40)
Fatigue on medium exertion	26 (19.3)
Tiredness upon heavy exertion	23 (17)
Persistent cough	3 (2.2)
Dermatological	78 (57.8)
Hair loss	44 (32.6)
Dermatitis	15 (11.1)
Hair loss and dermatitis	18 (13.3)
Musculoskeletal	72 (53.3)
Myoarticular pain	31 (23)
Muscle fatigue/weakness	32 (23.7)
Pain and fatigue and muscle weakness	8 (5.9)
Neurological	101 (74.8)
Memory loss	51 (37.8)
Concentration deficit	7 (5.2)
Memory loss and concentration deficit	40 (29.6)
Paresthesia of limbs	3 (2.2)
Psychological	102 (75.6)
Anxiety	65 (48.1)
Depression	9 (6.7)
Anxiety and depression	22 (16.3)
Irritability or stress	7 (5.2)
Activity and participation after COVID-19 infection	
Required help with self-care activities after COVID-19	27 (20)
Stopped performing activities (work, sports, and/or leisure) after COVID-19	47 (34.8)

SAH: Systemic Arterial Hypertension (Brazilian Guidelines on Systemic Arterial Hypertension).

case, the positive relationship is attributed to a greater amount of lean mass in the respiratory muscles.[16,17]

A Brazilian study carried out with individuals who did not require hospitalization due to COVID-19, and which also assessed pulmonary function, yielded results that were consistent with our findings. No pulmonary function disorders were observed when analyzing FVC and FEV1. One explanation for this may be that these were mild cases of COVID-19 that did not require support with positive pressure and supplementary oxygen. Despite the normal FVC and FEV1 findings, it is noteworthy that this did not exempt the patients from experiencing persistent symptoms, primarily respiratory, which can lead to functional impairment, affecting activity and participation.[18]

Patients who have not been hospitalized for COVID-19 exhibit persistent symptoms similar to those who have required hospitalization due to the disease. Cohort studies carried out with patients who required hospitalization during the acute phase and were evaluated 12 weeks after infection yielded similar results to the present study regarding the most prevalent

persistent symptoms reported by patients who did not require hospitalization, assessed 24 weeks after the disease: fatigue, dyspnea, and pain. Follow-up is crucial to ascertain the impact of these symptoms on non-hospitalized patients, enabling the provision of adequate care for those in need.[18,19]

A cohort comprising 958 individuals who were not hospitalized for COVID-19 investigated persistent symptoms between the sixth and eighth month after infection, reporting body pain in 13% of participants and hair loss in 5%, results that corroborate our findings. The mechanisms of the post-acute conditions of COVID-19 are not fully understood, but body pain and hair loss may be influenced by the excessive release of pro-inflammatory cytokines during the infectious period. Both symptoms may be impacted by the direct effects of the viral condition, social isolation, and the psychosocial state during post-COVID-19 recovery.[4,14]

Another cohort study conducted by Titze-de-Almeida et al. (2022), with patients who were not hospitalized, also assessed psycho-emotional symptoms, finding a prevalence of anxiety in 36.9% of the sample, corroborating our findings, in which psychological symptoms such as anxiety and depression were among the main persistent symptoms. Proportional values regarding symptoms related to difficulty concentrating and memory loss, as well as their persistence for more than five months after infection, were also found in both studies. Mental disorders have a multifactorial origin and can be triggered by environmental factors, such as the COVID-19 pandemic. Contracting the disease and the persistence of symptoms lead to a state of chronic stress that can impact basic cognitive processing, favoring deficits in memory and concentration.[20-22]

In our study, the participants faced limitations in performing activities of daily living after COVID-19 infection; i.e., some required assistance with these activities following infection. During self-reporting, the participants often expressed feeling the impact of symptoms, but did not consider it important to seek rehabilitation because they perceived such limitations as normal post-COVID-19. Some degree of physical limitation and the impact on the mental health of individuals after the course of an illness are expected, especially in those who already had some underlying condition. However, the potential consequences of these physical and psycho-emotional symptoms, such as an increased risk of mortality from clinical diseases, should not be overlooked.[23,24]

The literature is still limited regarding the follow-up of patients who have not required hospitalization due to COVID-19 infection but continue to experience persistent symptoms affecting their functionality, and consequently, their activity and participation. A strong point of this study is the significant number of mild cases of the disease in the sample, with respiratory muscle strength and lung function assessments conducted 6 months after recovery from the infection. Additionally, the symptoms were reported taking into account the perceptions of each individual. To the best of our knowledge, this is the second Brazilian study to evaluate lung function in patients who had COVID-19 and were not hospitalized, and the first to measure respiratory muscle strength in this population.

As a limitation, we acknowledge the absence of laboratory tests to explore possible correlations between biomarkers, persistent symptoms, and lung function.

After six months of recovery from COVID-19, individuals who did not require hospitalization due to the disease exhibited altered lung function, with reduced PEF, and respiratory muscle weakness, with reduced MEP.

Respiratory symptoms were the most persistent, particularly fatigue on exertion. In addition to respiratory symptoms, there were frequent reports of anxiety, depression, difficulty concentrating, and memory deficits, even six months after the disease. It is important to carry out studies on the impact of the persistence of these symptoms to understand their potential limitations in aspects of daily life, functionality, and quality of life.

AUTHOR CONTRIBUTIONS

BGS: data collection, writing, and descriptive analysis; ICS: writing and translation; RFC: data collection and writing; ERNR: data collection and writing; TRR: data collection and writing; JGSA: data collection and writing; EDBP: writing; NGC: data collection, writing, descriptive analysis, and translation.

REFERENCES

1. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J Med Virol. 2020 Abr;92(4):455–9. https://doi.org/10.1002/jmv.25688.
2. Zheng J. SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. Int J Biol Sci. 2020 Mar;16(10):1678–85. https://doi.org/10.7150/ijbs.45053.
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Mai;8(5):475–81. https://doi.org/10.1016/S2213-2600(20)30079-5.
4. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Ago;324(6):603–5. https://doi.org/10.1001/jama.2020.12603.
5. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology. 2020 Ago;296(2):E55–E64. https://doi.org/10.1148/radiol.2020200843.
6. Lazarin AC, Mariano RCZ, Marruaz AC, Pereira LC, Ganev ASM, Muradas MR, et al. Rede de Cuidados pós infecção humana pelo novo coronavírus (SARS-COV-2) – COVID-19 [Internet]. Campinas: Secretaria Municipal de Saúde; 2021 [citado 2023 Out]. 54 p. Disponível em: <https://covid-19.campinas.sp.gov.br/sites/covid-19.campinas.sp.gov.br/files/recomendacoes-tecnicas/Documento%203_RedeCuidadosPosCOVID-19_Edicao01_02jun21.pdf>.
7. Mitchell A, Chiwele I, Costello J. Coronavirus disease 2019

(COVID-19). BMJ Best Practice [Internet]. 2023 [citado 2023 Out]. Disponível em: https://bestpractice.bmj.com/topics/en-gb/3000201.

8. WHO. World Health Organization. Expanding our understanding of post COVID-19 condition: report of a WHO webinar [Internet]. Geneva: WHO; 2021 [citado 2023 Out]. 32 p. Disponível em: <https://iris.who.int/handle/10665/340951>.
9. Pessoa IMBS, Houri Neto M, Montemezzo D, Silva LAM, Andrade AD, Parreira VF. Predictive equations for respiratory muscle strength according to international and Brazilian guidelines. Braz J Phys Ther. 2014 Set–Out;18(5):410–8. https://doi.org/10.1590/bjpt-rbf.2014.0044.
10. Montemezzo D, Velloso M, Britto RR, Parreira VF. Maximal respiratory pressures: devices and procedures used by Brazilian physical therapists. Fisioter Pesqui. 2010 Jun;17(2):147–52. https://doi.org/10.1590/S1809-29502010000200010.
11. Trindade AM, Sousa TLF, Albuquerque ALP. The interpretation of spirometry on pulmonary care: until where can we go with the use of its parameters? Pulmão [Internet]. 2015 [citado 2023 Out];24(1):03-07. Disponível em: <https://www.sopterj.com.br/wp-content/themes/_sopterj_redesign_2017/_revista/2015/n_01/04.pdf>.
12. Kisiel MA, Janols H, Nordqvist T, Bergquist J, Hagfeldt S, Malinovschi A, et al. Predictors of post-COVID-19 and the impact of persistent symptoms in non-hospitalized patients 12 months after COVID-19, with a focus on work ability. Ups J Med Sci. 2022 Ago 9;127. https://doi.org/10.48101/ujms.v127.8794.
13. Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. Nat Med. 2022 Ago;28(8):1706–14. https://doi.org/10.1038/s41591-022-01909-w.
14. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. 2021 Jul;6:100122. https://doi.org/10.1016/j.lanepe.2021.100122.
15. José A, Malaguti C, Muller MG. Repercussões respiratórias e funcionais após infecção por COVID-19 [Internet]. Porto Alegre: Artmed Panamericana; 2020 [citado 2023 Out]. p. 9–29. Disponível em: <https://portal.secad.artmed.com.br/artigo/repercussoes-respiratorias-e-funcionais-apos-infeccao-por-covid-19>.
16. Simões RP, Deus APL, Auad MA, Dionísio J, Mazzonetto M, Borghi-Silva A. Maximal respiratory pressure in healthy 20 to 89 year-old sedentary individuals of central São Paulo State. Rev Bras Fisioter. 2010 Jan-Fev;14(1):60–7. https://doi.org/10.1590/s1413-35552010000100010.
17. Schoenberg JB, Beck GJ, Bouhuys A. Growth and decay of pulmonary function in healthy blacks and whites. Respir Physiol. 1978 Jun;33(3):367–93. https://doi.org/10.1016/0034-5687(78)90063-4.
18. de Oliveira JF, de Ávila RE, de Oliveira NR, da Cunha Severino Sampaio N, Botelho M, Gonçalves FA, et al. Persistent symptoms, quality of life, and risk factors in long COVID: a cross-sectional study of hospitalized patients in Brazil. Int J Infect Dis. 2022 Set;122:1044–51. https://doi.org/10.1016/j.ijid.2022.07.063.
19. Peghin M, Palese A, Venturini M, De Martino M, Gerussi V, Graziano E, et al. Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. Clin Microbiol Infect. 2021 Out;27(10):1507–13. https://doi.org/10.1016/j.cmi.2021.05.033.
20. Titze-de-Almeida R, da Cunha TR, Dos Santos Silva LD, Ferreira CS, Silva CP, Ribeiro AP, et al. Persistent, new-onset symptoms and mental health complaints in Long COVID in a Brazilian cohort of non-hospitalized patients. BMC Infect Dis. 2022 Fev;22(1):133. https://doi.org/10.1186/s12879-022-07065-3.
21. Jin Y, Sun T, Zheng P, An J. Mass quarantine and mental health during COVID-19: A meta-analysis. J Affect Disord. 2021 Dez;295:1335–46. https://doi.org/10.1016/j.jad.2021.08.067.
22. Dillon DG, Pizzagalli DA. Mechanisms of Memory Disruption in Depression. Trends Neurosci. 2018 Mar;41(3):137–49. https://doi.org/10.1016/j.tins.2017.12.006.
23. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive Meta-Analysis of Excess Mortality in Depression in the General Community Versus Patients With Specific Illnesses. Am J Psychiatry. 2014 Abr;171(4):453–62. https://doi.org/10.1176/appi.ajp.2013.13030325.
24. Hüfner K, Tymoszuk P, Ausserhofer D, Sahanic S, Pizzini A, Rass V, et al. Who Is at Risk of Poor Mental Health Following Coronavirus Disease-19 Outpatient Management? Front Med (Lausanne). 2022 Mar 14;9:792881. https://doi.org/10.3389/fmed.2022.792881.

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ORIGINAL ARTICLE

Relative incidence of interstitial lung diseases in Brazil

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Study carried out in the Universidade Federal de São Paulo and at the Clínica de Pneumologia CACP, both located in São Paulo (SP) Brasil; in the Universidade Federal de Minas Gerais and at the Hospital Julia Kubistchek, both located in Belo Horizonte (MG) Brasil; in the Universidade Federal de Goiás, located in Goiânia (GO) Brasil, and at the Hospital São Rafael, located in Salvador (BA) Brasil.

ABSTRACT

Objective: To assess the relative frequency of incident cases of interstitial lung diseases (ILDs) in Brazil. **Methods:** This was a retrospective survey of new cases of ILD in six referral centers between January of 2013 and January of 2020. The diagnosis of ILD followed the criteria suggested by international bodies or was made through multidisciplinary discussion (MDD). The condition was characterized as unclassifiable ILD when there was no specific final diagnosis following MDD or when there was disagreement between clinical, radiological, or histological data. **Results:** The sample comprised 1,406 patients (mean age = 61 ± 14 years), and 764 (54%) were female. Of the 747 cases exposed to hypersensitivity pneumonitis (HP)-related antigens, 327 (44%) had a final diagnosis of HP. A family history of ILD was reported in 8% of cases. HRCT findings were indicative of fibrosis in 74% of cases, including honeycombing, in 21%. Relevant autoantibodies were detected in 33% of cases. Transbronchial biopsy was performed in 23% of patients, and surgical lung biopsy, in 17%. The final diagnoses were: connective tissue disease-associated ILD (in 27%), HP (in 23%), idiopathic pulmonary fibrosis (in 14%), unclassifiable ILD (in 10%), and sarcoidosis (in 6%). Diagnoses varied significantly among centers ($\chi^2 = 312.4$; $p < 0.001$). **Conclusions:** Our findings show that connective tissue disease-associated ILD is the most common ILD in Brazil, followed by HP. These results highlight the need for close collaboration between pulmonologists and rheumatologists, the importance of detailed questioning of patients in regard with potential exposure to antigens, and the need for public health campaigns to stress the importance of avoiding such exposure.

Keywords: Lung diseases, interstitial/epidemiology; Alveolitis, extrinsic allergic/epidemiology; Connective tissue diseases/epidemiology, Sarcoidosis/epidemiology; Idiopathic pulmonary fibrosis/epidemiology

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of conditions that diffusely involve the lungs. Studies from several countries have shown that the frequency of the different types of ILDs varies widely.[1-13] In Brazil, hypersensitivity pneumonitis (HP) is a common ILD.[14]

A better understanding of the epidemiology of ILDs would enable the identification of possible risk factors and targets related to prevention and intervention. Additionally, it can help the health system make decisions about resource allocation that are of particular importance given the limited treatment options and the emergence of therapies that are often expensive.[15]

The accurate diagnosis of ILDs remains a challenge. The diagnostic criteria for the different diseases that comprise ILDs are amended and updated periodically, which makes epidemiological studies more difficult.[16,17] Two approaches are available in clinical practice for diagnosing ILDs: either a diagnosis based on strict clinical criteria, causing it not to be classified as specific ILDs in many cases; or a diagnosis based on clinical judgment, which results in fewer unclassifiable diseases. In many cases, there is a need for a multidisciplinary discussion (MDD) involving clinical, radiological, and pathological data.[18]

The present study evaluated the relative frequency of ILDs in Brazil using registries of incident cases in a multicenter setting and compared the findings with those observed in other countries.

METHODS

Study patients

This was a retrospective study involving six referral centers for ILD in Brazil (the Federal University of São Paulo and CACP Pulmonology Clinic, both located in the city of São Paulo; the Federal University of Minas Gerais and the Julia Kubistchek Hospital, both located in the city of Belo Horizonte; the Federal University of Goiás, located in the city of Goiânia; and the São Rafael Hospital, located in the city of Salvador). The study was approved by the

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Research Ethics Committee of the Federal University of São Paulo, the institution leading the research (Protocol no. 5.316.467), and by the committees of each center. The incident cases were consecutively identified between January 1, 2013, and January 31, 2020, from the medical records of patients diagnosed with ILD using a standardized evaluation sheet (see supplementary material; Chart S1).

Inclusion criteria

All participating centers had to be able to undertake a formal MDD with a pulmonologist experienced in ILDs, a thoracic radiologist, and a pulmonary pathologist, as well as to be able to perform ancillary procedures, including surgical lung biopsy (SLB) if necessary. There is no registration of referral centers for ILDs in the Brazilian Thoracic Society. We pooled a number of centers years ago, with the common goal of developing research studies. These groups standardized evaluation (Charts S1 and S2) and participated in periodic meetings with MDDs. In the present study, interstitial pneumonia with autoimmune features (IPAF) was included in the group of connective tissue diseases (CTDs).[19]

The central committee and the local centers reassessed undefined cases or cases with more than one possible diagnosis in an MDD. Several factors were considered in the initial diagnosis: the presence (or not) of CTD or relevant autoantibodies, systemic findings indicative of specific diseases, and biopsy reports from any site. Antinuclear antibodies (ANA), rheumatoid factor, anti-Ro, anti-LA, and anti-Jo1 were the most commonly measured antibodies. A positive family history was characterized by at least two cases of ILD among first-degree relatives, including the index case.[20] Because gastroesophageal reflux disease (GERD) is a common condition associated with various ILDs, an ILD was ascribed to GERD only when pH monitoring was abnormal in patients with bronchiolocentric fibrosis on SLB or HRCT in the absence of environmental exposure to organic antigens or CTD.

The distribution and predominance of tomographic findings and patterns were registered, as were age, gender, and environmental exposure history. Fibrosis identified by HRCT was characterized by reticular abnormalities with traction bronchiectasis or bronchiolectasis, with or without honeycombing. Drug-induced lung disease was characterized by the use of drugs potentially causing damage to the lungs preceding ILD, a compatible biopsy, or improvement after discontinuation of the suspected drugs.

CTDs were characterized in accordance with recent criteria.[21] Criteria suggested by the joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and other Granulomatous Disorders statement were applied for the diagnosis of sarcoidosis.[22]

The diagnosis of fibrotic HP were based on criteria suggested by the designated CHEST Guideline.[23] Antigen eviction, followed by a noticeable improvement in ILD, was considered a criterion for supporting the diagnosis of HP.[24] HP with no antigen exposure was only considered if SLB or a transbronchial lung biopsy displayed typical findings on analysis. The diagnoses of IPF were those suggested by a 2018 official clinical practice guideline.[17] In cases with honeycombing or reticulation on HRCT and exposure to a known antigen, patients ≥ 60 years of age and those < 60 years of age, respectively, were considered to have IPF and fibrotic HP, but other findings were also considered, such as a mosaic pattern on HRCT, elevated lymphocytes in BALF, and biopsy results. In the absence of such findings, a diagnosis of unclassifiable ILD was made.

The clinical diagnosis of unclassifiable ILD was characterized by insufficient data for a specific final diagnosis after detailed MDD, loss of follow-up, contraindications or patient refusal to SLB, or disagreement between clinical, radiological, and histological data.

Exclusion criteria

Patients with ILDs secondary to neoplastic diseases, infections, or heart disease were excluded from the study, as were cases with no HRCT results available during evaluation from the time of diagnosis (± 6 months), cases with inadequate HRCT image quality, and in those cases with no clinical or functional data for review or no MDD.

Statistical analysis

A proportion formula was used to calculate the sample size.[24] Assuming that 20% of the subjects in the population have the factor of interest, the study would require a sample size of 246 participants for estimating the expected proportion with 5% absolute precision and 95% confidence.[25]

Categorical variables were expressed as absolute and relative frequencies with 95% confidence intervals. The chi-square test was used in order to compare the frequency of categorical variables among groups.

RESULTS

The most common final diagnoses (> 1%) are shown in Figure 1. The most common diagnosis was CTD-associated ILD (CTD-ILD; 26.8%; 95% CI: 24.5-29.2), followed by HP (23.2%; 95% CI: 21.0-26.6), IPF (14.1%; 95% CI: 12.0-16.0), unclassifiable ILD (10.2%; 95% CI: 9.0-12.0); and sarcoidosis (6.3%; 95% CI: 5.1-8.0). The most common CTD-ILD was systemic sclerosis (31.2%), followed by rheumatoid arthritis (17.6%), IPAF (14.7%), Sjögren's syndrome (10.9%), autoimmune myositis (9.9%), and others (15.7%). The characteristics of the main ILD groups are described in the supplementary material (Table S1), as are the distribution according to the center of origin (Table S2) and according to the main ILD (Table S3).

The general characteristics of the 1,406 patients who comprised the sample are described in Table 1. There was a slight predominance of the female gender

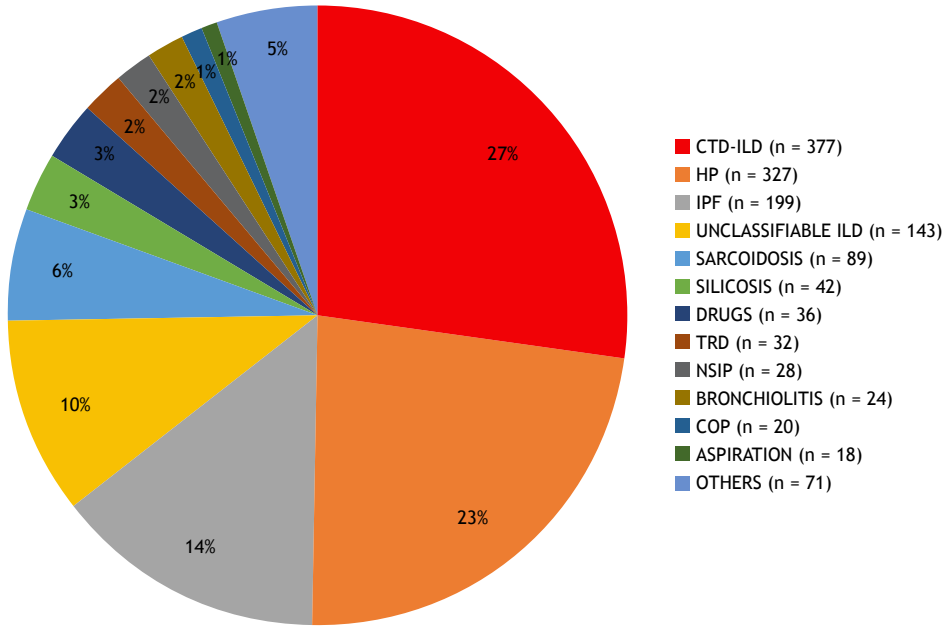

Figure 1. Distribution of the most commonly diagnosed interstitial lung diseases (ILDs) in a cohort of 1,406 cases in six centers in Brazil, 2013-2019. CTD-ILD: connective tissue disease-associated ILD; HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis, TRD: tobacco-related disease; NSIP: nonspecific interstitial pneumonia; and COP: cryptogenic organizing pneumonia.

(54%). The presence of exposure to organic antigens were common; 747 cases had potential exposure to HP-related antigens, but only 327 (44%) of these had a final diagnosis of HP. The major types of organic antigen exposure were to avian antigens and molds (Figure 2). Five patients who reported no exposure to known antigens were diagnosed with HP based on typical HRCT findings and bronchiolocentric fibrosis identified by SLB, and so were another 5 by SLB findings only. The major inorganic antigen were to silica, in 58 (4.6%); metals, in 13 (1.0%); and asbestos, in 10 (0.8%). Of those exposed to silica, 53% had a final diagnosis of silicosis. Of 1,293 patients questioned about GERD symptoms, 49% reported the presence of at least one. The final diagnosis of fibrosis due to microaspiration was made in 15 cases, 10 of which had bronchiolocentric fibrosis identified by SLB.

The use of drugs or radiation was noted in 253 cases, but a final diagnosis of drug-induced lung disease was made in only 36 (14.2%) of these cases—in 7 of 51 patients treated with amiodarone (13.7%), in 2 of 52 (3.8%) of those treated with methotrexate, and in 2 of 77 (2.5%) of those treated with statins. Radiation was the cause in 5 cases, and nitrofurantoin, in 3. Other causes were present in 17 cases.

Positive autoantibodies were seen in 398 of the 1,219 cases tested for autoantibodies (32.6%)—in isolation, in 23.2%, and in combination, in 9.6% (Table S4). ANA at a titer of 1:≥ 320 were observed in 31.4%, 8.7%, and 4.4% of patients with CTD, HP, and IPF, respectively. Anti-Ro antibodies, antisynthetase antibodies (including Jo-1), and anti-Scl 70 antibodies were present in 66 (5.4%), in 27 (2.1%), and in 42 (3.4%) of cases, respectively.

A family history of ILD was evaluated in 1,112 patients and was present in 8% of cases. Other relatives with ILD were present in 41 of the 160 cases of IPF (26.6%), in 42 of the 308 cases of HP (13.6%), in 13 of the 85 cases of unclassifiable ILD (15.3%), and in 10 of 306 (3.3%) of the cases of CTD ($\chi^2 = 87.1$; $p < 0.001$).

Previous or current smoking was reported by 66.5% of patients with IPF, by 54.5% of those with unclassifiable ILD, and by 44.1%, 36.8%, and 32.9% of those with HP, CTD-ILD, and sarcoidosis, respectively ($\chi^2 = 126.3$; $p < 0.001$).

HRCT findings indicative of fibrosis were found in 1,036 patients (73.7%), as were consolidation or ground glass pattern without fibrosis in 212 (20.3%), honeycombing in 301 (21.4%), and mosaic pattern in 209 (14.9%).

Transbronchial biopsy was performed in 323 patients (22.9%), and final or compatible diagnoses were achieved in 106 of these cases: sarcoidosis, in 23; HP, in 33; CTD-ILD, in 13; silicosis, in 11, and other diagnoses, in 26. SLB was performed in 241 (17.1%) of the patients, and results were inconclusive in 10 (4.1%), including 1 with findings of terminal lung only. Of the 231 remaining cases submitted to SLB, 58 (25.1%) had bronchiolocentric fibrosis, 52 (22.5%) had usual interstitial pneumonia, 41 (17.8%) had classic HP, 18 (7.8%) had diffuse alveolar damage, and 10 (4.3%) had bronchiolitis. Of the 52 biopsies from other sites, 36 were compatible with sarcoidosis, as were 11, 2, and 3 compatible with CTD-ILD, vasculitis, and other

Table 1. General characteristics of a cohort of patients with incident interstitial lung diseases at six centers in Brazil between 2013 and 2019 (N = 1,406).[a]

Variable	Result
Age, years	61.1 ± 13.9
Sex, female	764 (54.3)
Smoker or former smoker (n = 1,395)	657 (47.1)
Family history of ILD (n = 1,112)	112 (8.0)
Exposure to organic agents (n = 1,336)	747 (55.9)
Exposure to inorganic agents (n = 1,266)	164 (12.9)
Gastroesophageal reflux (n = 1,293)	634 (49.0)
Drugs (n = 1,321)	253 (19.1)
"Velcro" crackles (n = 1,367)	726 (53.1)
FVC, % predicted (n = 1,208)	68.0 ± 19.2

ILD: interstitial lung disease. [a]Values expressed as n (%) or mean ± SD.

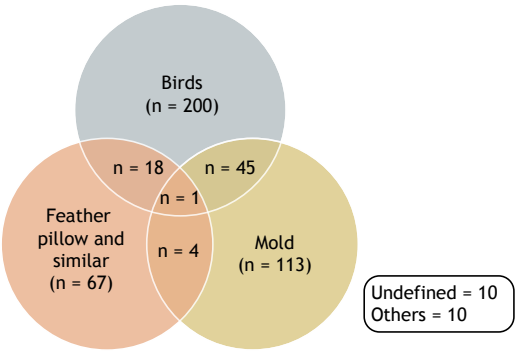

Figure 2. Distribution of the main types of exposure in the 327 cases of hypersensitivity pneumonitis.

diseases, respectively. Distribution of lung biopsy types by center is described in Table S5, as are the diagnostic yield of transbronchial biopsy in Table S6 and final diagnoses by SLB in Table S7.

Unclassifiable ILD was the final diagnosis in 10.2% of all cases. The mean age was 67.8 years; 67.4% were smokers or former smokers; and environmental exposure causing HP was present in 68.4% of cases, as were relevant autoantibodies in 13.8% and a familial history of ILD in 15.3%. With regard to HRCT findings, fibrotic disease was present in 90.9%, as was honeycombing in 20.3% of these. The main reasons for a diagnosis of unclassifiable ILD were incomplete data (in 55 cases), loss to follow-up (in 37 cases), and contraindications to SLB (in 35 cases). In 2 cases, SLB was inconclusive in 1 and unclassifiable in 1.

There was a statistically significant difference in final diagnoses among centers ($\chi^2 = 312.37$; $p < 0.001$), the proportion of CTD-ILD cases ranging from 15.0% to 38.2%; that of HP ranging from 13.2 to 36.5%; that of IPF ranging from 6.4% to 22.3%; that of unclassifiable ILD ranging from 3.1% to 18.9%, and that of sarcoidosis ranging from 0.0% to 9.4%.

The distribution of ILDs according to studies from several countries and to present study is shown in Figure 3. In New Mexico and in the Australasian registry,[6,12] IPF was the most common type of ILD, with 31.2% and 34% of cases, respectively. In Flanders and in most studies,[4,5,7,8,10,11,13] IPF (range, 18.2-38.6%) and sarcoidosis (range, 14.9-38.3%) were the most common ILDs. In studies carried out in China[3,9] and Saudi Arabia,[2] FPI and CTD-ILD were the most common ILDs. Only the Indian registry[1] showed that HP was the major ILD (47.3%), followed by CTD-ILD (13.9%).

DISCUSSION

In the present survey of 1,406 cases in six referral centers in Brazil, the most commonly diagnosed ILDs, in descending order, CTD-ILD, HP, IPF, unclassifiable ILD, and sarcoidosis.

IPF and sarcoidosis are the most common ILDs, but the frequency of the diagnoses of the various ILDs varies widely.[1-13] Several factors may explain these differences. One of these factors is the diagnostic criteria used for IPF, as these have changed in recent years.[16,17] The presence of autoimmune findings associated with the presence of ILD without definitive diagnostic criteria for a CTD was designated IPAF in 2015.[19] Today, it is recognized that there are several conditions within this group, including antisynthetase antibody syndrome, scleroderma sine scleroderma, and others. In the present study, IPAF was included in the classic CTD group.

In a single-center study conducted in Saudi Arabia, the most common ILDs were CTD-ILD (34.8%), followed by IPF (23.3%), sarcoidosis (20%), and HP (6.3%).[2] IPAF cases were included in the CTD group. Two studies conducted in China found that IPF was the most common diagnosis, followed closely by CTD-ILD.[3,9]

In the literature, the frequency of HP ranges from 1.5% to 47.3%, but in 9 of 13 studies,[1-13] this proportion was below 10%. An impressive proportion of 47.3% was observed in a prospective registry study undertaken in India, which included more than 1,000 patients.[1] Exposure to mold from the use of dirty air coolers or air conditioners or mold present at home, in addition to exposure to birds, were the most common types of exposure.[1]

A seminal study from Spain showed, in a case-cohort study, that in a sample of 46 patients with IPF, diagnosed according to the 2011 ATS/ERS/Japanese Respiratory Society (JRS)/*Asociación Latinoamericana de Tórax* (ALAT) guidelines, 20 (43%; 95% CI: 29-58%) had a subsequent diagnosis of chronic HP.[26] In a multicenter study, the diagnostic agreement among MDD teams in the diagnosis of IPF was good, but it was poor in that of HP.[27] This was attributed, at least in part, to the lack of guidelines for the diagnosis of HP. In 2020 and 2021, the ATS/JRS/ALAT and the *Chest* journal published guidelines for diagnosing HP, with some differences in the diagnostic criteria.[23,28]

In our study, antigens from molds, birds, and feather pillows were the most common causes for HP. Brazil is a country of continental dimensions with particular issues. Climatic conditions vary widely, and regions with high air humidity (forest and coastal regions and cities with frequent rain) increase mold exposure.[29]

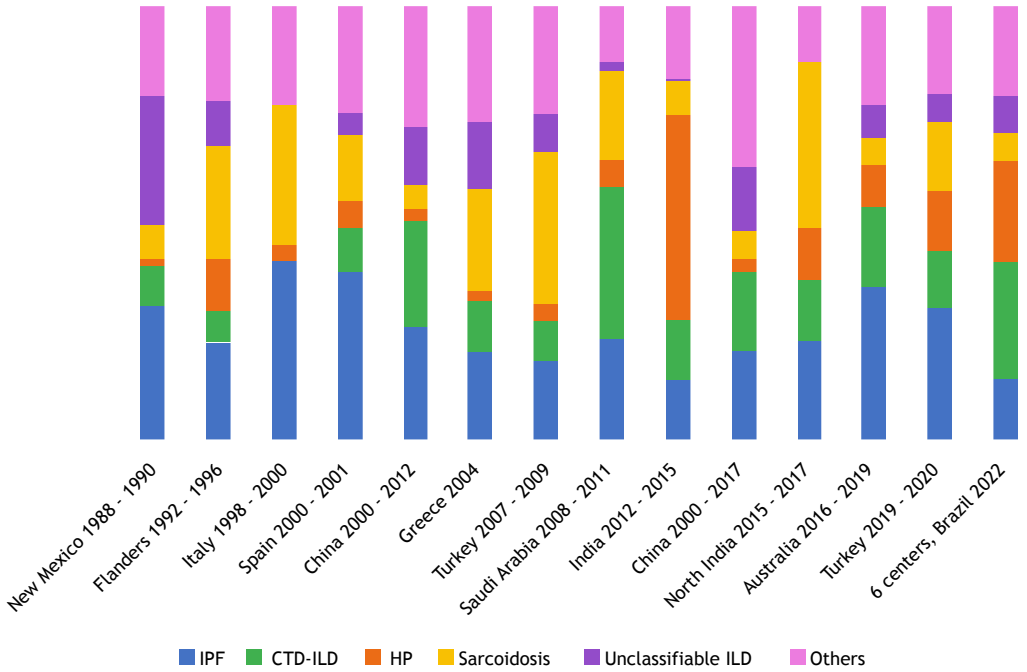

Figure 3. Distribution of interstitial lung diseases (ILDs) in different international prospective registry studies in comparison with the current study. IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-associated ILD; and HP: hypersensitivity pneumonitis.

Socioeconomic conditions vary widely too. Many people live in poor housing with damp indoor spaces. In Brazil, there are about 41.3 million captive birds.[30]

In the literature, several studies show a large proportion of cases diagnosed as HP with no apparent exposure to antigens.[31] In contrast, in our study, 53% of the total number of patients with ILDs displayed potential exposures to HP-related antigens. However, the number of patients with a final diagnosis of HP in this group was only 44%. In our survey, only 10 (3%) of HP cases were diagnosed with no apparent antigen exposure.

Unclassifiable ILD comprises a heterogeneous group of diseases.[32] In the present study, the incidence of unclassifiable ILD was 10.2%. A meta-analysis of 22 studies reported that the prevalence of unclassifiable ILD was 11.9% (95% CI: 8.5-15.6), with a lower prevalence in centers that reported the use of a formal MDD (9.5% vs. 14.5%).[32] In our study, 15.3% of cases of unclassifiable ILD were cases of familial ILD. In many cases of familial ILD, atypical findings on HRCT and in pathology specimens can be identified, making the diagnosis more difficult.[33,34] The incidence of sarcoidosis was 6.3% in the present study. In comparison with prevalence studies, a lower proportion is expected due to a better prognosis of sarcoidosis.[35] Moreover, the incidence and prevalence of sarcoidosis vary across regions and even within countries.[35] In Brazil, the epidemiology of sarcoidosis is largely unknown.

In this study, ILD was attributed to drugs or radiation in 2.6% of cases. Although statins and methotrexate were used by many patients, less than 5% of the cases of ILD were considered to be caused by these drugs. The relationship between methotrexate and the lung seems to be twofold. Methotrexate can induce unpredictable subacute granulomatous pneumonitis, but it seems not to be associated with an increased risk of chronic fibrotic ILD in rheumatoid arthritis, and perhaps it even reduces that risk.[36] Symptoms of GERD were very common in ILD patients, but in only 15 cases was GERD the final diagnosis ascribed to microaspiration. In 10 cases, bronchiolocentric fibrosis was characterized by SLB.

Given the fact that ILD may complicate the course of any CTD, and that ILD can precede signs of CTD, and these signs can be subtle, an underlying CTD should be ruled out in every ILD, even if clinical suspicion is low or absent. Autoantibody screening should be performed in patients with ILD with an unclear diagnosis after careful clinical evaluation. Although autoantibodies can be found in conditions other than CTD, ANA and rheumatoid factor in significant levels can be seen in HP, and ANA can also be seen in patients with IPF.[37,38] Recently, greater importance has been given to the panel of autoantibodies related to autoimmune myositis that are frequently associated with ILD. However, at the time of data collection, this panel was scarcely available.[39]

Registry studies have strengths and limitations. The main advantage is that data from a large number of cases are available, making it possible to estimate the incidence of diseases within a narrow margin of error, especially when well-defined criteria are applied to

the diagnosis and reviewed by a central committee, as was the case in the current study; however, some limitations should be noted. First, data were collected in a "real-life" scenario, and such data were missing in several patients. Second, the patients were treated at referral centers for ILDs, which may have resulted in selection bias. The variation across centers in the proportions for individual entities deserves future studies.

In conclusion, in this sample of patients in Brazil, the most common types of ILD were, in decreasing order, CTD-ILD, HP, IPF, and sarcoidosis. In 10% of cases, the disease was unclassifiable. These results highlight the need for close collaboration between pulmonologists and rheumatologists, the need for detailed questioning of patients regarding potential exposures that may result in HP, the importance of public health campaigns to make people aware of the dangers of such exposures, and the need for more stringent workplace regulations to protect employees from environmental exposures. Understanding the epidemiology of ILDs in Brazil allows the health care system to make informed decisions about mastering allocation of resources to meet local needs, which are of particular importance in the era of emerging ILD therapies, which often have high costs.[40]

AUTHOR CONTRIBUTIONS

SLKM and CACP: conceptualization, data curation, formal analysis, investigation, project administration, and drafting, reviewing, and editing of the manuscript. MRS and EVM: formal analysis (support), and reviewing and editing of the manuscript. FCVF, MACM, FMAB, TAP, and GCJ: data collection. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, et al. Interstitial Lung Disease in India. Results of a Prospective Registry. Am J Respir Crit Care Med. 2017;195(6):801-813. https://doi.org/10.1164/rccm.201607-1484OC
2. Alhamad EH. Interstitial lung diseases in Saudi Arabia: A single-center study. Ann Thorac Med. 2013;8(1):33-37. https://doi.org/10.4103/1817-1737.105717
3. Guo B, Wang L, Xia S, Mao M, Qian W, Peng X, et al. The interstitial lung disease spectrum under a uniform diagnostic algorithm: a retrospective study of 1,945 individuals. J Thorac Dis. 2020;12(7):3688-3696. https://doi.org/10.21037/jtd-19-4021
4. Thomeer M, Demedts M, Vandeurzen K; VRGT Working Group on Interstitial Lung Diseases. Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta Clin Belg. 2001;56(3):163-172. https://doi.org/10.1179/acb.2001.026
5. Xaubet A, Ancochea J, Morell F, Rodriguez-Arias JM, Villena V, Blanquer R, et al. Report on the incidence of interstitial lung diseases in Spain. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21(1):64-70.
6. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994 Oct;150(4):967-72. https://doi.org/10.1164/ajrccm.150.4.7921471
7. Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopoulou A, et al. Epidemiology of interstitial lung diseases in Greece. Respir Med. 2009;103(8):1122-1129. https://doi.org/10.1016/j.rmed.2009.03.001
8. Agostini C, Albera C, Bariffi F, De Palma M, Harari S, Lusuardi M, et al. First report of the Italian register for diffuse infiltrative lung disorders (RIPID). Monaldi Arch Chest Dis. 2001;56(4):364-368.
9. Ban C, Yan W, Xie B, Zhu M, Liu Y, Zhang S, et al. Spectrum of interstitial lung disease in China from 2000 to 2012. Eur Respir J. 2018;52(3):1701554. https://doi.org/10.1183/13993003.01554-2017
10. Musellim B, Okumus G, Uzaslan E, Akgün M, Cetinkaya E, Turan O, et al. Epidemiology and distribution of interstitial lung diseases in Turkey. Clin Respir J. 2014;8(1):55-62. https://doi.org/10.1111/crj.12035
11. Dhooria S, Agarwal R, Sehgal IS, Prasad KT, Garg M, Bal A, et al. Spectrum of interstitial lung diseases at a tertiary center in a developing country: A study of 803 subjects. PLoS One. 2018;13(2):e0191938. https://doi.org/10.1371/journal.pone.0191938
12. Moore I, Wrobel J, Rhodes J, Lin Q, Webster S, Jo H, et al. Australasian interstitial lung disease registry (AILDR): objectives, design and rationale of a bi-national prospective database. BMC Pulm Med. 2020;20(1):257. https://doi.org/10.1186/s12890-020-01297-2
13. Aycicek O, Cetinkaya E, Demirci Ucsular F, Bayram N, Senyigit A, Aksel N, et al. Research Burden of Interstitial Lung Diseases in Turkey - RBILD. Sarcoidosis Vasc Diffuse Lung Dis. 2022;39(1):e2022006.
14. Pereira CA, Gimenez A, Kuranishi L, Storrer K. Chronic hypersensitivity pneumonitis. J Asthma Allergy. 2016;9:171-181. https://doi.org/10.2147/JAA.S81540
15. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in Global Prevalence of Interstitial Lung Disease. Front Med (Lausanne). 2021;8:751181. https://doi.org/10.3389/fmed.2021.751181
16. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824. https://doi.org/10.1164/rccm.2009-040GL
17. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44-e68. https://doi.org/10.1164/rccm.201807-1255ST
18. Ryerson CJ, Corte TJ, Lee JS, Richeldi L, Walsh SLF, Myers JL, et al. A Standardized Diagnostic Ontology for Fibrotic Interstitial Lung Disease. An International Working Group Perspective. Am J Respir Crit Care Med. 2017;196(10):1249-1254. https://doi.org/10.1164/rccm.201702-0400PP
19. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976-987. https://doi.org/10.1183/13993003.00150-2015
20. Kropski JA. Familial Interstitial Lung Disease. Semin Respir Crit Care Med. 2020;41(2):229-237. https://doi.org/10.1055/s-0040-1708054
21. Corte TJ, Wells AU. Connective tissue diseases. In: Broadus VC, Ernst JD, King Jr TE, Lazarus SC, Sarmiento KF, Schnapp LM, et al. editors. Murray & Nadel's Textbook of Respiratory Medicine. 7th ed, Philadelphia: Elsevier; 2022, p.1262-1283.
22. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J. 1999;14(4):735-737. https://doi.org/10.1034/j.1399-3003.1999.14d02.x
23. Fernández Pérez ER, Travis WD, Lynch DA, Brown KK, Johannson KA, Selman M, et al. Diagnosis and Evaluation of Hypersensitivity Pneumonitis: CHEST Guideline and Expert Panel Report. Chest. 2021;160(2):e97-e156. https://doi.org/10.1016/j.chest.2021.03.066
24. Statutator [homepage on the Internet]. Sydney, Australia: Statutator; c2023 [cited 2023 Jul 1]. Sample Size Calculator for Estimating a Single Proportion. Available from: https://www.statulator.com/SampleSize/ss1P.html
25. Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. N Engl J Med.

2018;378(19):1811-1823. https://doi.org/10.1056/NEJMra1705751

26. Morell F, Villar A, Montero MÁ, Muñoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. Lancet Respir Med. 2013;1(9):685-694. https://doi.org/10.1016/S2213-2600(13)70191-7
27. Walsh SLF, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, et al. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir Med. 2016;4(7):557-565. https://doi.org/10.1016/S2213-2600(16)30033-9
28. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2021 Jan 1;203(1):150-151] [published correction appears in Am J Respir Crit Care Med. 2022 Aug 15;206(4):518]. Am J Respir Crit Care Med. 2020;202(3):e36-e69. https://doi.org/10.1164/rccm.v206erratum4
29. Brasil Escola [homepage on the Internet]. Goiânia: Brasil Escola; c2023 [cited 2023 Jul 1]. Umidade do ar [about 20 screens]. Available from: https://brasilescola.uol.com.br/geografia/umidade-ar.htm
30. ABINPET [homepage on the Internet]. São Paulo: ABINPET; c2023 [cited 2023 Jul 1]. Mercado Pet Brasil 2023. [Adobe Acrobat document, 11p.]. Available from: https://abinpet.org.br/wp-content/uploads/2023/05/abinpet_folder_dados_mercado_2023_draft5.pdf
31. Trushenko NV, Suvorova OA, Pershina ES, Nekludova GV, Chikina SY, Levina IA, et al. Predictors of Progression and Mortality in Patients with Chronic Hypersensitivity Pneumonitis: Retrospective Analysis of Registry of Fibrosing Interstitial Lung Diseases. Life (Basel). 2023;13(2):467. https://doi.org/10.3390/life13020467
32. Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ. Heterogeneity in Unclassifiable Interstitial Lung Disease. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2018;15(7):854-863. https://doi.org/10.1513/AnnalsATS.201801-067OC
33. Leslie KO, Cool CD, Sporn TA, Curran-Everett D, Steele MP, Brown KK, et al. Familial idiopathic interstitial pneumonia: histopathology and survival in 30 patients. Arch Pathol Lab Med. 2012;136(11):1366-1376. https://doi.org/10.5858/arpa.2011-0627-OAI
34. Baratella E, Ruaro B, Giudici F, Wade B, Santagiuliana M, Salton F, et al. Evaluation of Correlations between Genetic Variants and High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis. Diagnostics (Basel). 2021;11(5):762. https://doi.org/10.3390/diagnostics11050762
35. Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: Epidemiology and clinical insights. J Intern Med. 2023;293(6):668-680. https://doi.org/10.1111/joim.13629
36. Cottin V, Bendstrup E, Bonniaud P, Nasser M, Spagnolo P, Valenzuela C, et al. The case of methotrexate and the lung: Dr Jekyll and Mr Hyde. Eur Respir J. 2021;57(2):2100079. https://doi.org/10.1183/13993003.00079-2021
37. Adegunsoye A, Oldham JM, Demchuk C, Montner S, Vij R, Strek ME. Predictors of survival in coexistent hypersensitivity pneumonitis with autoimmune features. Respir Med. 2016;114:53-60. https://doi.org/10.1016/j.rmed.2016.03.012
38. Araiza MT, Aguilar León DE, Retana VN, Martínez-Cordero E. IgM, IgG, and IgA rheumatoid factors in pigeon hypersensitivity pneumonitis. J Clin Lab Anal. 2007;21(5):315-321. https://doi.org/10.1002/jcla.20188
39. Bahmer T, Romagnoli M, Girelli F, Claussen M, Rabe KF. The use of auto-antibody testing in the evaluation of interstitial lung disease (ILD)–A practical approach for the pulmonologist. Respir Med. 2016;113:80-92. https://doi.org/10.1016/j.rmed.2016.01.019
40. Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in Global Prevalence of Interstitial Lung Disease. Front Med (Lausanne). 2021;8:751181. https://doi.org/10.3389/fmed.2021.751181

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ORIGINAL ARTICLE

Role of the *IL8* rs4073 polymorphism in central nervous system toxicity in patients receiving multidrug-resistant tuberculosis treatment

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ABSTRACT

Objective: To determine the role of the *IL8* rs4073 polymorphism in predicting the risk of central nervous system (CNS) toxicity in patients receiving standard pharmacological treatment for multidrug-resistant tuberculosis (MDR-TB). **Methods:** A cohort of 85 consenting MDR-TB patients receiving treatment with second-line antituberculosis drugs had their blood samples amplified for the *IL8* (rs4073) gene and genotyped. All patients were clinically screened for evidence of treatment toxicity and categorized accordingly. Crude and adjusted associations were assessed. **Results:** The chief complaints fell into the following categories: CNS toxicity; gastrointestinal toxicity; skin toxicity; and eye and ear toxicities. Symptoms of gastrointestinal toxicity were reported by 59% of the patients, and symptoms of CNS toxicity were reported by 42.7%. With regard to the genotypes of *IL8* (rs4073), the following were identified: AA, in 64 of the study participants; AT, in 7; and TT, in 11. A significant association was found between the dominant model of inheritance and CNS toxicity for the crude model (p = 0.024; OR = 3.57; 95% CI, 1.18-10.76) and the adjusted model (p = 0.031; OR = 3.92; 95% CI, 1.13-13.58). The AT+TT genotype of *IL8* (rs4073) showed a 3.92 times increased risk of CNS toxicity when compared with the AA genotype. **Conclusions:** The AT+TT genotype has a tendency to be associated with an increased risk of adverse clinical features during MDR-TB treatment.

Keywords: Tuberculosis, multidrug-resistant; Immunity; Pharmacogenetics; Polymerase chain reaction; Risk.

INTRODUCTION

Tuberculosis disease is very common in poor countries with a high population of HIV-infected individuals, malnourished individuals, or both. Nigeria is one of the countries with the highest tuberculosis burden, with a prevalence of 830,000 cases.[1,2] A poor tuberculosis infection control program is characterized by low (below-expected) rates of disease diagnosis and insufficient or inadequate treatment of diagnosed tuberculosis, leading to treatment failure,[1] which can be attributed to poor treatment compliance or a lack of effective drugs available in the national health care systems.[3] Treatment failure is most pronounced in patients diagnosed with multidrug-resistant tuberculosis (MDR-TB). Approximately 45% of all treated cases reportedly fail to achieve a successful outcome, and this category of treatment outcome has an enormous role in the continued persistence of tuberculosis disease.[4] Another very important factor contributing to poor treatment compliance and treatment failure is the adverse drug reaction (ADR) commonly associated with tuberculosis treatment. It is of note that there are numerous potential ADRs, such as hepatotoxicity, cardiotoxicity, and nephrotoxicity, which could actually be detected by tests incorporated into a holistic tuberculosis management protocol. Routine liver enzyme testing, assessment of renal function biomarkers, and echocardiography can be incorporated into the tuberculosis management protocol in order to allow early detection. A sizable number of patients express frustration with their antituberculosis medications and stop taking them well before any objective findings suggesting toxicity.[5] Thus, identifying clinical symptoms that may herald the manifestation of a devastating ADR may provide an early predictor of the ADR.

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Neurotoxicity, which can be central or peripheral, initially manifests via a number of very wide-ranging clinical features, including headache, blurred vision, tremors, dizziness, tinnitus, and poor coordination.[6-9] Other severe and highly morbid manifestations of neurotoxicity include seizure, loss of vision, ataxia, psychosis, myoclonus, and delirium.

Increased perspiration, rashes, dry skin, and itching are common early features of skin-related antituberculosis drug toxicity, whereas Stevens-Johnson syndrome is a life-threatening feature.[10] Antituberculosis drugs can cause reversible blurred vision, and permanent visual impairment can occur in severe cases.[11,12]

There is a clear difference among patients regarding the occurrence of ADRs. Some of the risk factors for ADRs are well known, whereas others have yet to be identified.[13] In addition to establishing an accurate diagnosis of tuberculosis, identifying risk factors for individual differences in ADRs in patients receiving tuberculosis treatment is very important to avoid iatrogenic drug injury in susceptible patients.

Polymorphisms in drug-metabolizing genes such as *NAT2*, *GSTM1*, *GSTT1*, and *CYP2E1* have been implicated in the considerably complex variability of antituberculosis drug levels and their effects, including ADRs.[13,14] It is well known that environmental factors can modify the effects of these pharmacogenetic variations on the metabolism of antituberculosis drugs.[13] A number of pharmacogenetic studies have investigated the role of genetic polymorphisms of proinflammatory cytokines such as TNF, IL-6, and IL-8 in first-line tuberculosis treatment outcomes such as ADRs.[14-16] It is also well established that the human genome has a number of common genetic variants that are in linkage disequilibrium and that are inheritable, being inherited in unison along with all of the yet to be identified genetic variants responsible for the clinical phenotypes (disease/treatment outcome—efficacy or ADR).[17] Thus, the well-established drug-metabolizing enzyme gene loci associated with antituberculosis drugs might be in linkage with the gene loci of proinflammatory cytokines.[17-19] The impetus for the present study was the dearth of pharmacogenomic studies assessing ADRs to second-line antituberculosis drugs, which are more toxic by nature, especially with regard to neurotoxicity, which is not monitored by periodic serological testing in the management of tuberculosis. In addition, the current WHO global action framework for tuberculosis research encourages patient-oriented tuberculosis research and innovations at country level, especially in low- and middle-income countries.[3,18]

METHODS

Study location and design

The study design was approved by the Kano State Ministry of Health Research Ethics Committee (NHREC/17/03/2018). Tuberculosis patients were recruited among those receiving hospital-based MDR-TB treatment and those receiving MDR-TB treatment in a community care setting in Kano, Nigeria. The study assessed associations of single nucleotide polymorphisms with clinical phenotypes of toxicity following MDR-TB treatment with second-line antituberculosis drugs. Clinical toxicities were assessed by the Patient-Rated Inventory of Side Effects and included gastrointestinal symptoms such as nausea, vomiting, constipation, diarrhea, abdominal pain, and loss of appetite, as well as central nervous system (CNS) symptoms such as dizziness, drowsiness, headache, poor coordination, restlessness, and tremors.

A cohort of 85 patients diagnosed with and receiving treatment for MDR-TB were enrolled in this study. The MDR-TB treatment regimen used in our clinic included levofloxacin, bedaquiline, ethionamide, cycloserine, delamanid, pyrazinamide, meropenem, linezolid, and moxifloxacin. Patients received the WHO-recommended doses, always in accordance with weight, BMI, or both.[20] All patients were diagnosed at a tuberculosis center by a trained physician using WHO-recommended diagnostic criteria. MDR-TB was defined as a positive Xpert MTB/RIF assay result (Cepheid, Sunnyvale, CA, USA). The inclusion criteria were as follows: laboratory and/or genetic evidence of MDR-TB at the onset of therapy; evidence of optimal adherence to and completion of treatment with second-line antituberculosis drugs; having no immunodeficiency or other diseases; and being in the 18- to 80-year age bracket. The exclusion criteria were as follows: being very ill and incapable of providing written informed consent; having no documented evidence of an MDR-TB diagnosis; currently receiving treatment with first-line antituberculosis drugs; having no documented evidence of compliance with treatment; being pregnant; having hepatitis; and having declined to give written informed consent.

Five milliliters of peripheral venous blood were collected from consenting participants after completion of treatment, with the use of a 5-mL syringe fitted with an appropriate sized 18-G needle. The blood was anticoagulated with 0.5% EDTA (pH = 8.0) by placing it in an EDTA tube. Genomic DNA was extracted by using a whole blood genomic DNA extraction kit (QIAGEN, Hilden, Germany) in accordance with the manufacturer instructions, with an appropriate quantity of molecular-grade ethanol (Sigma-Aldrich, Burlington, MA, USA), being stored at −20°C for later use.

The genotypes of *IL8* (rs4073) were amplified by using the appropriate identified forward primer: 5′-ATCTTGTTCTAACACCTGCCACTC-3′ and reverse primer 5′-TAAAATACTGAAGCTCCACAATTTGG-3′ in the reaction mixture. The reaction mixture was made up to a total volume of 25 µL containing 12.5 µL of DreamTaq Green PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), 5 µL of template DNA, 1 µL of upstream primer, 1 µL of downstream primer, and 5.5 µL of RNase-free water. The PCR cycling conditions consisted of an initial denaturation step at 94°C for 5 min, followed by 35 cycles at 94°C for 50

s, 61°C for 60 s, and 72°C for 55 s, followed by a final extension step at 72°C for 5 min. The PCR product was digested with the MfeI restriction enzyme (Thermo Fisher Scientific) at 37°C for 2 h and deactivated at 80°C for 20 min. The digested PCR product was analyzed by 2% agarose gel electrophoresis, set up in ultrapure grade Tris-acetate-EDTA buffer solution, visualized under ultraviolet illumination, scanned, and photographed.[21]

Sample size calculation

For the current study, the sample size was calculated for a power of 80% and a level of significance of 5% to identify an OR difference of at least two-fold (OR = 2) in the distribution of genotypes for MDR-TB, which has a prevalence of 32% in Nigeria.[22] The estimates from the literature were substituted into the Schlesselman formula for sample size calculation:

$$M = m/Pe$$

where m = (((Z1-a/2/2 + Z1-b) (P*(1-P*))1/2)2 / (P*-0.5)2; P* = OR/(1 + OR); Pe (probability of exposure-discordant pair) = (p1(1-p0) + p0(1-p1); p1(proportion of exposed individuals developing case) = p0 (OR)/1 + p0 (OR-1); and p0 = exposure rate among controls in populations.

The estimated sample size for cases and controls was 30 each, for a total of 60 (m = 14.495; Pe = 0.118; P* = 0.667; p1 = 0.485; M = 30).

RESULTS

The sociodemographic characteristics of the study participants are described in Table 1. The study participants were mostly poor (n = 74; 87.06%), even though they earned some income through their jobs (n = 77; 90.59%). The mean age of the participants was 31.88 ± 11.51 years. Most were of the Hausa ethnic group, were Muslims (Islam), were employed, and were from low-income families (Table 1).

With regard to the clinical characteristics of the study participants, more than 22.5% had a history of tuberculosis/MDR-TB, a history of tuberculosis treatment, a family history of tuberculosis, or any combination of the three. As can be seen in Table 2, the study participants reported the following MDR-TB treatment-related symptoms: gastrointestinal symptoms, sleep symptoms, CNS symptoms, skin symptoms, cardiovascular symptoms, and urinary tract symptoms. CNS symptoms included the following: headache (in 9.8%), tremors (in 14.6%), poor coordination (in 2.4%), and dizziness (in 11%). Gastrointestinal symptoms included the following: vomiting/nausea (in 30.1%), diarrhea (in 7.2%), and constipation (in 2.4%). Blurred vision and ringing in the ears (tinnitus) were also reported (by 7.2% and 13.3%, respectively).

With regard to the genotypes of *IL8* (rs4073), the following were identified: AA (wild-type homozygous), in 64 of the study participants; AT (wild-type heterozygous), in 7; and TT (homozygous), in 11 (Table 3). None of the genotypes of *IL8* (rs4073) were significantly associated with ADR phenotypes, the exception being the phenotype of CNS toxicity. Table 3 shows the distribution of the genotypes of *IL8* (rs4073) by inheritance model and CNS toxicity phenotype.

A significant association was found between the dominant model of inheritance and the binary dependent variable (presence or absence of ADRs involving the CNS) for the crude model (p = 0.024; OR = 3.57; 95% CI, 1.18-10.76) and the adjusted model (p = 0.031; OR = 3.92; 95% CI, 1.13-13.58; Table 3). The AT+TT genotype of *IL8* (rs4073) showed a 3.92 times increased risk of CNS toxicity when compared with the AA genotype.

DISCUSSION

In our sample of patients with MDR-TB, there were more males than females (n = 58 vs. n = 28), and the numbers of married and unmarried participants were the same (n = 41 for both). The religious and ethnic characteristics of the study participants were consistent with those predominantly seen in the population of Kano State, Nigeria. The predominance of individuals with low income and an elementary level of education in our sample of patients with MDR-TB was similar to what is observed in other areas where tuberculosis is endemic. A significant association was found between the dominant model of inheritance of *IL8* (rs4073) genotypes and CNS toxicity. The presence of the T allele (in the AT+TT genotype) significantly increased the risk of CNS toxicity (by 3.92 times).

To the best of our knowledge, our finding of an association between genotypes of *IL8* (rs4073) and CNS toxicity is a novel result. Although earlier studies have assessed the association of *IL8* rs4073 with phenotypes of tuberculosis disease, there have been no studies assessing the association of *IL8* (rs4073) with phenotypes of treatment-related ADRs. There have been reports of an association between *IL8* (rs4073) and other medical conditions, including breast cancer and autoimmune thyroid disease.[23,24] In the aforementioned studies,[23,24] the TT genotype was associated with a higher risk of breast cancer or autoimmune thyroid disease than was the AA genotype. In another study,[25] the *IL8* (rs4073) polymorphism was assessed in its dominant, recessive, and allele models, and was associated with a risk of developing pulmonary tuberculosis disease. Thus, there is a similarity in the role of the TT genotype between our study and other studies in the literature regarding its tendency to be associated with an increased risk of adverse clinical features, despite the difference in the clinical features assessed; the aforementioned studies assessed breast cancer, tuberculosis, and autoimmune thyroid disease, whereas our study assessed symptoms of CNS toxicity. The precise mechanism by which this polymorphism influences the development of

Table 1. Sociodemographic characteristics of the study participants.

Characteristic	MDR-TB patients receiving treatment (N = 82)
Age	31.88 ± 11.51
Sex (M/F)	54/28
Marital status (never married/once married)	41/41
Ethnicity (H/Y/I/O)	79/0/1/2
Religion (Islam/Christianity)	78/4
Job status(earning/dependent)	67/15
Family income (low income/high income)	74/8
Educational level (elementary/advanced)	66/16
Family history of tuberculosis (no/yes)	62/18
History of tuberculosis (no/yes)	59/23
History of tuberculosis treatment (no/yes)	72/10

MDR-TB: multidrug-resistant tuberculosis; H: Hausa; Y: Yoruba; I: Igbo; and O: other.

Table 2. Adverse drug reactions commonly reported by patients receiving treatment for multidrug-resistant tuberculosis in Kano State, Nigeria.

Toxicity	Symptom	N (%)	With ADRs, n	Without ADRs, n
Gastrointestinal toxicity	Nausea/vomiting	25 (30.1%)	50	33
	Diarrhea	6 (7.2%)		
	Constipation	2 (2.4%)		
	Dry mouth	17 (20.5%)		
Eye and ear toxicities	Blurred vision	6 (7.2%)	17	66
	Ringing in the ears	11 (13.3%)		
Central nervous system toxicity	Headache	8 (9.8%)	35	47
	Tremors	12 (14.6%)		
	Poor coordination	2 (2.4%)		
	Dizziness	11 (11.0%)		
Skin toxicity	Increased perspiration	2 (2.4%)	31	52
	Dry skin	10 (12.0%)		
	Rash	9 (10.8%)		
	Itching	10 (12.0%)		

ADRs: adverse drug reactions; N: total sample size; and n: sample sizes based on different categories.

Table 3. Statistical assessment of the association of genotypes of the *IL8* rs4073 (A>T) polymorphism in different inheritance models with phenotypes of toxicity.

		CNS ADRs	No CNS ADRs	Crude estimate	Adjusted estimate
Codominant model	TT[a]	7	4	-	-
	AA	23	41	p = 0.094; OR = 0.321 (95% CI, 0.085-1.212); R^2_N = 0.088	p* = 0.070; OR = 0.26 (95% CI, 0.06-1.11); R^2_N = 0.230
	AT	5	2	p = 0.733; OR = 1.429 (95% CI, 0.184-11.085); R^2_N = 0.088	p = 0.959; OR = 1.063 (95% CI, 0.106-10.632); R^2_N = 0.230
Overdominant model	AT	5	2	p* = 0.128; OR = 3.750 (95% CI, 0.683-20.602); R^2_N = 0.042	p* = 0.240; OR = 3.24 (95% CI, 0.455-23.04); R^2_N = 0.178
	AA+TT[a]	30	45		
Dominant model	AA[a]	23	41	p = 0.024; OR = 3.57 (95% CI, 1.18-10.76); R^2_N = 0.086	p* = 0.031; OR = 3.92 (95% CI, 1.13-13.58); R^2_N = 0.230
	AT+TT	12	6		
Recessive model	AA+AT[a]	28	43	p = 0.141; OR = 2.687 (95% CI, 0.720-10.035); R^2_N = 0.036	p* = 0.097; OR = 3.350 (95% CI, 0.81-13.94); R^2_N = 0.200
	TT	7	4		

CNS: central nervous system; ADRs: adverse drug reactions; and R^2_N: Nagelkerke's R^2. Note: Age, sex, ethnicity, marital status, educational level, family income, and type of job were the covariates used for adjusted estimates. [a]Reference category. *Statistically significant.

diseases such as breast cancer, tuberculosis, and autoimmune thyroid disease has yet to be elucidated. Understandably, the role of the genotypes in the development of toxicities of second-line antituberculosis drugs has yet to be established as well. However, the mechanism by which cytokines contribute to toxicity in any organ might be similar to the mechanisms of hepatotoxicity. Hepatotoxicity is the most studied toxicity mechanism for antituberculosis drugs, and the identified mechanisms of hepatotoxicity might be similar to those of other toxicities. It develops directly from the drug metabolites or indirectly via immune mediation.[26] Thus, the delicate balance between proinflammatory and anti-inflammatory cytokines plays a vital role in the progression of immune-mediated tissue injury. The anti-inflammatory mechanisms in the liver suppress the activities and production of proinflammatory factors such as TNF-α, IFN-c, IL-1, and IL-8, thus limiting the progression of hepatotoxicity.[27] In the same vein, the anti-inflammatory role of IL-8, which is abundantly secreted by neutrophils, antigen-presenting cells such as oligodendrocytes, and Schwann cells may putatively underlie its role in the development of toxicity in the CNS and other tissues. Furthermore, the activities of the proximal promoter region of the *IL8* (rs4073) gene that modulates the transcriptional level of its proteins encoded by (four) exons interspersed within three intron regions may explain its role in the interindividual variability attributable to its different genotypes at the polymorphic site.[28] The aforementioned putative explanation appears very plausible and is in keeping with the finding of the current study, i.e., that the AT+TT genotype increases the risk of CNS toxicity. Nevertheless, a thorough mechanistic evaluation must be carried out for validation purposes.

One of the limitations of the current study was that we did not assess the association between the symptoms of CNS toxicity and the genotypes of the different drug-metabolizing enzymes. Future studies assessing the association of genotypes of drug-metabolizing enzymes and *IL-8* (rs4073) with symptoms of toxicity could identify the presence or absence of linkage disequilibrium for these gene loci.

In conclusion, this study demonstrated an association between the *IL8* rs4073 gene polymorphism and symptoms of CNS toxicity in MDR-TB patients receiving treatment with standard second-line drugs. This association must be confirmed by controlled studies.

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AUTHOR CONTRIBUTIONS

IBM, IAA, MAG, IAU, and JS developed the concept of the study. AUA, U-AMM, MM, OJ, I-MK, IBM, and IAU were involved in data collection. AUA, U-AMM, I-MK, and IBM were involved in genotyping. AUA, U-AMM, I-MK, IBM, JS, and MAG were involved in data analysis. All authors reviewed the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Harshavardhan S, Vijayakumar KK, Sounderrajan V, Ramasamy P, Rajadas SE. Basics of tuberculosis disease and principles of treatment and their effects. In: Rajan M, editor. A Mechanistic Approach to Medicines for Tuberculosis Nanotherapy. London: Academic Press; 2021. p. 1-29. https://doi.org/10.1016/B978-0-12-819985-5.00011-5
2. Dinic L, Akande P, Idigbe EO, Ani A, Onwujekwe D, Agbaji O, et al. Genetic determinants of drug-resistant tuberculosis among HIV-infected patients in Nigeria. J Clin Microbiol. 2012;50(9):2905-2909. https://doi.org/10.1128/JCM.00982-12
3. Gonzalez Y, Guzmán-Beltrán S, Carreto-Binaghi LE, & Juárez E. Translational research for therapy against tuberculosis. In: Kesharwani P, editor. Nanotechnology Based Approaches for Tuberculosis Treatment. London: Academic Press; 2020. p. 53-73.doi:10.1016/b978-0-12-819811-7.00004-7 https://doi.org/10.1016/B978-0-12-819811-7.00004-7
4. World Health Organization. Global Health TB Report. Geneva: World Health Organization; 2018. ISBN 978-92-4-156564-6
5. Kaona FA, Tuba M, Siziya S, Sikaona L. An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment. BMC Public Health. 2004;4:68. https://doi.org/10.1186/1471-2458-4-68
6. Girling DJ. Adverse effects of antituberculosis drugs. Drugs. 1982;23(1-2):56-74. https://doi.org/10.2165/00003495-198223010-00003
7. Owens RC Jr, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis. 2005;41 Suppl 2:S144-S157. https://doi.org/10.1086/428055
8. Schwartz MT, Calvert JF. Potential neurologic toxicity related to ciprofloxacin. DICP. 1990;24(2):138-140. https://doi.org/10.1177/106002809002400204
9. Narita M, Tsuji BT, Yu VL. Linezolid-associated peripheral and optic neuropathy, lactic acidosis, and serotonin syndrome. Pharmacotherapy. 2007;27(8):1189-1197. https://doi.org/10.1592/phco.27.8.1189
10. Kass JS, Shandera WX. Nervous system effects of antituberculosis therapy. CNS Drugs. 2010;24(8):655-667. https://doi.org/10.2165/11534340-000000000-00000
11. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167(4):603-662. https://doi.org/10.1164/rccm.167.4.603
12. Menon V, Jain D, Saxena R, Sood R. Prospective evaluation of visual function for early detection of ethambutol toxicity. Br J Ophthalmol. 2009;93(9):1251-1254. https://doi.org/10.1136/bjo.2008.148502

13. Costa GN, Magno LA, Santana CV, Konstantinovas C, Saito ST, Machado M, et al. Genetic interaction between NAT2, GSTM1, GSTT1, CYP2E1, and environmental factors is associated with adverse reactions to anti-tuberculosis drugs. Mol Diagn Ther. 2012;16(4):241-250. https://doi.org/10.1007/BF03262213
14. Mattingly CJ, Rosenstein MC, Davis AP, Colby GT, Forrest JN Jr, Boyer JL. The comparative toxicogenomics database: a cross-species resource for building chemical-gene interaction networks. Toxicol Sci. 2006;92(2):587-595. https://doi.org/10.1093/toxsci/kfl008
15. García-Elorriaga G, Carrillo-Montes G, Mendoza-Aguilar M, González-Bonilla C. Polymorphisms in tumor necrosis factor and lymphotoxin A in tuberculosis without and with response to treatment. Inflammation. 2010;33(4):267-275. https://doi.org/10.1007/s10753-010-9181-8
16. Peresi E, Oliveira LR, da Silva WL, da Costa EA, Araujo JP Jr, Ayres JA, et al. Cytokine Polymorphisms, Their Influence and Levels in Brazilian Patients with Pulmonary Tuberculosis during Antituberculosis Treatment. Tuberc Res Treat. 2013;2013:285094. https://doi.org/10.1155/2013/285094
17. Motsinger AA, Ritchie MD. Multifactor dimensionality reduction: an analysis strategy for modelling and detecting gene-gene interactions in human genetics and pharmacogenomics studies. Hum Genomics. 2006 Mar;2(5):318-28. https://doi.org/10.1186/1479-7364-2-5-318
18. Piras D, Zoledziewska M, Cucca F, Pani A. Genome-Wide Analysis Studies and Chronic Kidney Disease. Kidney Dis (Basel). 2017;3(3):106-110. https://doi.org/10.1159/000481886
19. Deguchi T. Physiology and molecular biology of arylamine N-acetyl transferases. Biomed Res. 1992;13:231-242. https://doi.org/10.2220/biomedres.13.231
20. World Health Organization. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug- Resistant Tuberculosis. Geneva: World Health Organization; 2014. Available from: https://ncbi.nlm.nih.gov/books/NBK247420/?term=Companion%20Handbook%20to%20the%20WHO%20Guidelines%20for%20the%20Programmatic%20Management%20of%20Drug-%20Resistant%20Tuberculosis
21. Wu CC, Huang YK, Huang CY, Shiue HS, Pu YS, Su CT, et al. Polymorphisms of TNF-α -308 G/A and IL-8 -251 T/A Genes Associated with Urothelial Carcinoma: A Case-Control Study. Biomed Res Int. 2018;2018:3148137. https://doi.org/10.1155/2018/3148137
22. Onyedum CC, Alobu I, Ukwaja KN. Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and meta-analysis. PLoS One. 2017;12(7):e0180996. https://doi.org/10.1371/journal.pone.0180996
23. Zhang J, Han X, Sun S. IL-8 -251A/T and +781C/T polymorphisms were associated with risk of breast cancer in a Chinese population. Int J Clin Exp Pathol. 2017;10(7):7443-7450.
24. Akahane M, Watanabe M, Inoue N, Miyahara Y, Arakawa Y, Inoue Y, et al. Association of the polymorphisms of chemokine genes (IL8, RANTES, MIG, IP10, MCP1 and IL16) with the pathogenesis of autoimmune thyroid diseases. Autoimmunity. 2016;49(5):312-319. https://doi.org/10.3109/08916934.2015.1134507
25. Holt MP, Ju C. Mechanisms of drug-induced liver injury. AAPS J. 2006;8(1):E48-E54. https://doi.org/10.1208/aapsj080106
26. Bourdi M, Masubuchi Y, Reilly TP, Amouzadeh HR, Martin JL, George JW, et al. Protection against acetaminophen-induced liver injury and lethality by interleukin 10: role of inducible nitric oxide synthase. Hepatology. 2002;35(2):289-298. https://doi.org/10.1053/jhep.2002.30956
27. Chen J, Ma A. Associations of polymorphisms in interleukins with tuberculosis: Evidence from a meta-analysis. Immunol Lett. 2020;217:1-6. https://doi.org/10.1016/j.imlet.2019.10.012
28. Hacking D, Knight JC, Rockett K, Brown H, Frampton J, Kwiatkowski DP, et al. Increased in vivo transcription of an IL-8 haplotype associated with respiratory syncytial virus disease-susceptibility. Genes Immun. 2004;5(4):274-282. https://doi.org/10.1038/sj.gene.6364067

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SPECIAL ARTICLE

Lung cancer screening in Brazil: recommendations from the Brazilian Society of Thoracic Surgery, Brazilian Thoracic Association, and Brazilian College of Radiology and Diagnostic Imaging

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ABSTRACT

Although lung cancer (LC) is one of the most common and lethal tumors, only 15% of patients are diagnosed at an early stage. Smoking is still responsible for more than 85% of cases. Lung cancer screening (LCS) with low-dose CT (LDCT) reduces LC-related mortality by 20%, and that reduction reaches 38% when LCS by LDCT is combined with smoking cessation. In the last decade, a number of countries have adopted population-based LCS as a public health recommendation. Albeit still incipient, discussion on this topic in Brazil is becoming increasingly broad and necessary. With the aim of increasing knowledge and stimulating debate on LCS, the Brazilian Society of Thoracic Surgery, the Brazilian Thoracic Association, and the Brazilian College of Radiology and Diagnostic Imaging convened a panel of experts to prepare recommendations for LCS in Brazil. The recommendations presented here were based on a narrative review of the literature, with an emphasis on large population-based studies, systematic reviews, and the recommendations of international guidelines, and were developed after extensive discussion by the panel of experts. The following topics were reviewed: reasons for screening; general considerations about smoking; epidemiology of LC; eligibility criteria; incidental findings; granulomatous lesions; probabilistic models; minimum requirements for LDCT; volumetric acquisition; risks of screening; minimum structure and role of the multidisciplinary team; practice according to the Lung CT Screening Reporting and Data System; costs versus benefits of screening; and future perspectives for LCS.

Keywords: Lung neoplasms; Early detection of cancer; Tomography, X-ray computed; Tobacco use disorder.

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INTRODUCTION

Lung cancer screening (LCS) using low-dose CT (LDCT) of the chest has become the gold standard in the preventive approach to the population at high risk for lung cancer (LC). Over the last decade, various countries have adopted periodic population screening with LDCT as a public health recommendation, following the guidelines of specialized medical societies.

In Brazil, albeit still incipient, discussion on this topic is increasingly broad and necessary. To expand the knowledge of and stimulate debate regarding LCS, the *Sociedade Brasileira de Cirurgia Torácica* (SBCT, Brazilian Society of Thoracic Surgery), the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association), and the *Colégio Brasileiro de Radiologia e Diagnóstico por Imagem* (CBR, Brazilian College of Radiology and Diagnostic Imaging) convened a panel of experts to prepare these initial recommendations.

These recommendations are intended for all medical professionals involved in caring for patients with risk factors for LC. The group that conceived and coordinated the recommendations, including members from the SBCT, SBPT, and CBR, presented questions and general themes to the panel of 21 experts, who, in virtual meetings, defined the most relevant topics to be covered.

Each theme or question was written by two or three of the authors, on the basis of a narrative review of the current, most relevant evidence in the literature and internationally accepted guidelines. That was followed by two phases of text harmonization. In the first, four experts discussed and restructured the texts sent by the others, and, in the second, all of the experts reviewed, discussed, and validated the final text.

CONCEPTS ABOUT SCREENING AND WHY TO SCREEN

- Diagnosing LC at an early stage reduces mortality and healthcare costs.
- In organized screening, the target population is invited and monitored at a defined periodicity, within an examination quality program and decision flowcharts.
- These are challenges for implementing screening programs in Brazil:
  - Budgetary limitations
  - Heterogeneity in the distribution of human resources and equipment
  - Sociocultural barriers
  - Lack of public health policies appropriate to the levels of prevention

Despite the growing number of advances in the diagnosis and treatment of LC, there are an estimated 2.2 million new cases and more than 2 million deaths each year worldwide, with an estimated 31,270 new cases and 27,000 deaths in Brazil.[1,2] Of the new cases in Brazil, only 15% are diagnosed in stage I, which is potentially curable[3]; that translates to an overall five-year survival rate of less than 20%.

The clinical results in LC are directly related to the stage of cancer at the time of diagnosis. Screening and early detection significantly reduces the mortality associated with the disease. The impact can go beyond that, including lower public health expenditures, because the cost of treatment is lower for patients with early-stage LC than for those with advanced-stage LC.[4]

Screening is characterized by the application of tests in asymptomatic individuals, in a defined target population, with the aim of reducing the morbidity and mortality attributed to a specific disease.[5] The WHO classifies screening as one of two types:

1. Opportunistic—Examinations are carried out on the basis of patient demand or are offered by the health care professional during a health care visit.
2. Organized—The target population is invited and monitored at a defined frequency, within a quality program for examinations and following decision flow charts.

Screening for various cancers, such as prostate, skin, breast, uterine, and colorectal cancer, has been a reality for decades. Combining LCS with multidisciplinary management can also be cost-effective and is one of the best alternatives to minimize the consequences. However, it remains a major challenge in various countries, including high-income countries, where it is still limited in comparison with the screening for other neoplasms.

To diagnosis LC early and reduce mortality, a number of studies conducted in recent decades have evaluated LCS strategies. Initial protocols based on sputum smear cytology and chest X-ray proved to be innocuous.[6] Studies based on the Early Lung Cancer Action Project[7] and International Early Lung Cancer Action Project trials,[8] designated the ELCAP and IELCAP trials, respectively, have shown LDCT to be a method that is sensitive, safe, and feasible for early diagnosis. That was confirmed in 2011 by studies employing data from the National Lung Screening Trial (NLST),[9,10] which evaluated 53,454 high-risk volunteers, demonstrating a rate of positivity (positive nodule ≥ 4 mm) on LDCT of 39%, with confirmation of LC in 1% and a 20% reduction in cancer mortality.[9,10]

Some studies of LCS in Europe, with smaller sample sizes, did not show significant differences in LC mortality or overall mortality.[11-14] In Brazil, a prospective study, designated the First Brazilian Lung Cancer Screening Trial (BRELT1),[15] evaluated 790 volunteers with eligibility criteria similar to those of the NLST and showed the occurrence of positive findings to be 46% higher than in the NLST, with biopsies performed in 3.1% of the patients and cancer diagnosed in approximately 1.3%. The BRELT1[15] demonstrated that, despite there being a greater number of nodules > 4 mm, the prevalence of neoplasia was similar to that reported in the NLST.[9,10]

In 2020, the results of a study conducted in the Netherlands and Belgium, designated the NELSON trial (Registration no. NL580),[16] with a sample of 15,792 volunteers, showed a rate of positivity on LDCT (positive nodule: 500 mm^3, approximately 10 mm) of 6.5%, and LC was confirmed in 2.1% of the cases evaluated. The NELSON trial also showed that, over a period of 10 years, there were reductions in the risk of death from cancer of 24% in men and more than 60% in women.[16]

A systematic review of data from 84,558 volunteers up to 2020, showed a 17% reduction in the risk of death from LC, albeit without evidence of a reduction in overall mortality.[17]

A more recent study, designated the BRELT2,[18] evaluated 3,470 individuals undergoing screening with LDCT at six different centers in Brazil. In that study sample, the prevalence of LC was 2.1%. It is noteworthy that, in 51% of those cases, LC was diagnosed at an early stage. The data confirm that, despite the obstacles, LCS is feasible in Brazil, with results similar to those reported for other countries.

Based on this evidence, international societies and expert panels began to recommend performing LCS with LDCT, although questions regarding feasibility, cost-effectiveness, and access still stand between the recommendations and the practical implementation of this strategy, especially in public health care systems.[19,20]

The use of LCS assumes that symptomatic disease is preceded by a period of presymptomatic disease detectable by LDCT. The interval of time between detection by screening and the time at which the neoplasm would be detected by the onset of its clinical manifestations is called the lead time (LT). According to most estimates, LT values for LC detection by LDCT range from 0.9 years to 3.5 years. Real-world studies that report mortality after LC diagnosis are subject to the so-called LT bias, although adjustments to the methods, aimed at minimizing that bias, have been proposed.[21]

A more adequate assessment of NLST data should also consider overdiagnosis and LT bias. The magnitude of overdiagnosis depends critically on the duration of follow-up after final screening.[21] In the NLST, the maximum follow-up period was initially 7 years but was later extended to 11.3 years.[9,10] After that extension, the overdiagnosis rate during the entire NLST period, originally predicted to be zero, was 3%. Using life expectancy gain instead of adjusting (for LT bias) for the expected number of lives saved overestimated the efficacy of life expectancy gain in the NLST by 38%.[21]

There are still a number of challenges to overcome before screening programs can be implemented in Brazil, such challenges including budgetary limitations, as well as the heterogeneous distribution of human resources and equipment in the public and private health care systems. In addition, cultural barriers, between patients and between physicians, indicate the need to construct health policies that encompass approaches aimed at each level of prevention.[22,23]

GENERAL CONSIDERATIONS ABOUT SMOKING

- In Brazil, 9.3% of adults are smokers.
- Smoking cessation increases the efficacy of screening programs.
- Stopping smoking reduces the risk of complications and mortality from chronic diseases, including cancer, as well as increasing life expectancy and quality of life.
- The foundations of smoking cessation are determination, behavioral support, and pharmacological treatment.

Smoking is the leading cause of chronic noncommunicable diseases and causes dozens of types of cancer, being responsible for more than 85% of all cases of LC.[24,25]

Tobacco can be consumed without combustion, by using *snus* or snuff, or with combustion and smoke inhalation, by using cigars, pipes, cigarettes, or hookahs.[26,27] In recent years, the use of electronic smoking devices (ESDs) has skyrocketed in many countries, including Brazil.[28-34] Although they release fewer substances harmful to health, new generations of ESDs release aerosols with greater amounts of nicotine, heavy metals, and fine particulate matter than do regular cigarettes, with cardiovascular and respiratory risks, as well as risks of cancer and death.[29,35] One recent study detected nearly 2,000 substances in ESDs,[36] and another showed that ESD users are at a three times greater risk of becoming smokers of regular cigarettes than are individuals who have never used an ESD.[37]

The proportion of individuals who consume tobacco products worldwide is trending downward for the first time in decades; it was 23.6% in 2020.[38] Tobacco control policies instituted in Brazil a few decades ago helped to substantially reduce tobacco consumption rates, according to the Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases, from 35% in the 1980s to 9.3% in 2023.[34,39-41]

In 2015, cigarette smoking in Brazil resulted in the expenditure, in Brazilian reals (R$), of R$56.9 billion related to health care, disability, and deaths, whereas only R$12.9 billion were collected in the form of taxes on the manufacture and sale of tobacco products.[42]

Quitting smoking increases life expectancy, improves quality of life, and reduces the risks/complications associated with dozens of diseases, as well as reducing health care costs.[43,44] Smoking cessation also reduces LC mortality by a magnitude comparable to that of screening (20%), and the reduction is even greater (38%) when both strategies are implemented.[45] In addition, survival after surgical treatment for early-stage LC is better among patients who have

quit smoking than among those who have not.[46] Therefore, it is essential to identify smokers and incorporate smoking cessation strategies into LCS protocols.

Quitting smoking is not an easy task, because of the combination of physical dependence, psychological dependence, and conditioning.[44,47-50] Smoking cessation treatment is based on the decisiveness/determination and motivation of the smoker, together with behavioral counseling and support (BCS) and the use of first-line medications.[43,44,47-50]

The foundations of BCS are the identification of situations that create a risk of relapse and the development of coping strategies through skills training. That support can be provided through a brief/minimal approach, in just a few minutes, by any and all health care professionals during routine care, and consists in interviewing, evaluating, and advising smokers in order to prepare them to quit smoking, comprising a basic approach, in which patients are monitored for the first few weeks after quitting smoking, and an intensive approach, in which at least seven sessions, each lasting at least 10 min, are held at specialized facilities.[43,44,47-50]

First-line medications are divided into two groups[43,44,48-50]: nicotinic medications, collectively known as nicotine replacement therapy (NRT), including nicotine patches, gum, and lozenges; and non-nicotinic medications, including bupropion, antidepressants, and varenicline, the last being a nicotinic receptor inhibitor that is temporarily unavailable in several countries, including Brazil.

The success rate of treatment with bupropion is similar to that of NRT, and both have success rates lower than that achieved through treatment with varenicline.[51-54] The choice of medications is individualized, monotherapy is generally sufficient, and the usual duration of treatment is 3 months. Combining more than one medication can increase the success rate in patients who have greater difficulty in quitting smoking.[48-53,55] Recently issued guidelines recommend the use of varenicline or the combination of two NRTs as the first option to initiate treatment for patients with heart disease, lung disease, or cancer.[56-58]

Because ESDs are not medications for smoking cessation, first-line medications should be preferred,[55,59] and the majority of smokers who stop smoking by switching to an ESD continue to use ESDs, which perpetuates their dependence on nicotine and increases the health risks they face.[60]

In Brazil, intensive smoking cessation treatment can be provided via the *Sistema Único de Saúde* (SUS, Unified Health Care System), free of charge, at primary health care clinics in municipalities; via some supplementary health care networks; and via private physician offices and clinics.

BASIC ASPECTS AND EPIDEMIOLOGY OF LC

- Smoking continues to be the main cause of LC.
- LC is one of the most common and lethal types of tumor.
- Only 15% of LCs are diagnosed at an early stage, when they are potentially curable.

For decades, smoking has been the most relevant risk factor for LC. Therefore, some of the most effective tobacco control measures are counseling to avoid taking up the habit of smoking, especially for young people, and advising current smokers to stop smoking as soon as possible.

There are two main types of LC: small-cell lung cancer and non-small-cell lung cancer (NSCLC). More than 80% of all cases of LC are NSCLC, which is divided into three subtypes[61]: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma.

A retrospective cohort study in Brazil showed a 30% decrease in the proportion of cases of small-cell lung cancer between the 1997-2002 and 2002-2008 periods.[62] Another nationwide epidemiological study involving more than 35,000 cases of NSCLC reported a change among the NSCLC subtypes in Brazil from 2003 onwards—adenocarcinomas accounting for 43.3% of cases and squamous-cell carcinomas accounting for 36.5%.[63]

Worldwide, LC is the leading cancer in men and the third leading cancer in women; in Brazil, it is the third leading cancer in men and the fourth leading cancer in women, with the exception of non-melanoma skin cancer.[64] In Brazil, 31,270 new cases of LC and approximately 27,000 LC-related deaths are recorded annually.[2] Only 15% of patients with LC are diagnosed at an early stage, when the disease is potentially curable, which translates to an overall five-year survival rate

Table 1. Stages of lung cancer at diagnosis in studies carried out in Brazil.

Authors	N	Type of institution	NSCLC	Early stage (I/II)
Ismael et al.[62]	1,887	Public	89%	16%
Younes et al.[66]	737	Public	100%	22.5%
Costa et al.[67]	3,167	Public	90.8%	13.3%
Westphal et al.[68]	352	Public	91%	19%
Barros et al.[69]	263	Public	87%	6%
Novaes et al.[70]	240	Public	80%	28.2%
Araujo et al.[71]	566	Private	100%	20.4%
Mascarenhas et al.[72]	338	Private	83%	21.8%

NSCLC: non-small-cell lung cancer.

of less than 20% (Table 1).[62,65-72] Therefore, despite advances in diagnosis and staging—mainly in clinical treatment (targeted therapies and immunotherapy) and surgical treatment (video-assisted surgery and robotics)—the morbidity and mortality associated with LC remains high, as do its personal, family, public health, and supplementary health costs.

One of the reasons for a tumor being diagnosed at an advanced stage is the delay in diagnostic procedures via the SUS, such as CT and PET/CT, which are difficult to access in some regions of Brazil.[61]

In 2006, Barros et al.[69] reported that only 20% of patients with suspected LC had access to diagnostic CT. Nearly 90% of the patients in their cohort were diagnosed by chest X-ray.[69] Another study conducted in Brazil estimated that the median time from the onset of symptoms to diagnosis is 3 months.[73] That situation becomes even more complicated because few public health care facilities provide diagnostic procedures such as bronchoscopy and transthoracic biopsy.[61] The implementation of screening programs in the SUS will facilitate the development of regional LC diagnostic services in Brazil.

SCREENING ELIGIBILITY CRITERIA

- Eligibility criteria
  - Being a smokers/former smoker, being ≥ 50 years of age, and having a smoking history > 20 pack-years
- Exclusion criteria
  - Being > 80 years age
  - Having quit smoking > 15 years prior
  - Having symptoms suggestive of or a history of LC
  - Having a functional status or comorbidity that precludes curative treatment

The most important benefit of LCS is the increase in the number of cases diagnosed at an early stage (stage I or II) and the consequent reduction in that of those diagnosed at an advanced stage (stage III or IV).[74]

Studies using NLST data have demonstrated that LC-related mortality, in three annual rounds, was significantly lower when LCS employed LDCT than when it employed chest X-ray.[9,10] The incidence rate was 0.85, and the number needed to screen (NNS) to prevent one death was 323 over 6.5 years of follow-up.[10] Another study demonstrated a reduction in LC-related mortality in four rounds of follow-up, with an incidence rate of 0.75, and the NNS to prevent one death was 130 over 10 years of follow-up.[75]

Although there are variations in the inclusion criteria for LCS, the main international recommendations are based on the two largest trials (the NLST and the NELSON trial),[7,9,14-16,76-82] as detailed in Table 2.

On the basis of previous studies and microsimulation models, the U.S. Preventive Services Task Force (USPSTF) established, in 2013, guidelines for "real life" screening in the United States,[74,75] with the following inclusion criteria: being 55-74 years of age; having a smoking history of at least 30 pack-years; and having quit smoking less than 15 years prior.

At that time, the USPSTF guidelines did not take into account interracial differences in smoking patterns and LC risk, as had previously been demonstrated.[83,84] A few years after the screening program had been implemented in real-life scenarios (outside of clinical studies), it became obvious that there was a need to take such differences into account.

Aldrich et al.[85] found that the proportion of individuals diagnosed with LC who would not have been eligible for screening in the United States was higher among African-American smokers than among White smokers. That is because African-Americans typically develop LC with a smoking history of less than 30 pack-years and before 55 years of age. Therefore, it has been suggested that the smoking history criterion be reduced to 20 pack-years and that the age criterion be reduced to 50 years. Those new criteria were promptly adopted by the USPSTF and the National Comprehensive Cancer Network.[86,87]

Given such evidence, this panel of experts recommends that the inclusion criteria for LDCT screening consist of the following:

- Being a smoker or former smoker, ≥ 50 years of age
- Having a smoking history of more than 20 pack-years or having quit smoking less than 15 years prior

Screening should be discontinued when the volunteer is over 80 years of age or has been smoke-free for more than 15 years.

The exclusion criteria for screening are as follows[85-87]:

- The presence of symptoms highly suggestive of LC
- A history of LC
- Functional status or comorbidity that would prevent treatment with curative intent, given that the patient must be fit to undergo lung resection

It is recommended that the decision to start the screening program be shared between the individual and the multidisciplinary team, and that all smokers be encouraged to participate in BCS programs to quit smoking. That should permeate all consultations; it should be borne in mind that screening is not a substitute for smoking cessation.

The greatest challenge is still establishing the definition of a high-risk patient and, therefore, determining the inclusion criteria so that annual screening is even more cost-effective. In brief, it is necessary to improve the criteria for selecting asymptomatic individuals exposed to the main risk factors for LC, given that the relative risk of developing the disease increases in parallel with advancing age.

It is worth highlighting, however, that the recommendations above were based on population-level data from other countries. There is a need for studies on the appropriateness of these positivity criteria for use in the population of Brazil.

Table 2. National and international studies of lung cancer screening.

Authors	Study acronym	Participants*	Inclusion criteria	Positivity n (%)**	Biopsy n (%)	LC n (%)
National Lung Screening Trial Research Team et al.[9]	NLST	26,722	A 55-74 y; CS or FS (SF ≤ 15 y); SH ≥ 30 p-y	7,191 (27)	758 (2.8)	270 (1.0)
de Koning et al.[16]	NELSON	6,583	A 50-74 y; CS or FS (SF ≤ 12 y); SH ≥ 30 p-y	467 (2.1)	-	203 (0.9)
Henschke et al.[7]	ELCAP	1,000	A ≥ 60 y; SH ≥ 10 p-y; no previous cancer; clinically fit for thoracic surgery	233 (23)	28 (2.8)	27 (2.7)
Gohagan et al.[76]	LSS	1,586	A 55-74 y; CS or FS (SF ≤ 10 y); and SH ≥ 30 p-y	325 (21)	57 (3.6)	30 (1.9)
Wilson et al.[77]	PLuSS	3,642	A 50-79 y; CS or FS (SF ≤ 15 y); smoked ≥ 25 y and ≥ 10 cig/day; and body weight < 180 kg	1,477 (41)	90 (2.5)	36 (1.0)
Infante et al.[14]	DANTE	1,276	Male; A 60-74 y; CS or FS (SF < 10 y); and SH ≥ 20 p-y	199 (15)	52 (4.1)	28 (2.2)
Lopes Pegna et al.[78]	ITA LUNG	1,406	A 55-69 y; CS or FS (SF ≤ 10 y); and SH ≥ 20 p-y	426 (30)	22 (1.6)	21 (1.5)
Saghir et al.[79]	DLCST	2,052	A 50-70 y; CS or FS (SF < 10 y and > 50 y of A); SH ≥ 20 p-y; able to climb 36 steps without stopping	594 (29)	25 (1.2)	17 (0.8)
Becker et al.[80]	LUSI	2,029	A 50-69 y; CS or FS (SF ≤ 10 y); smoked ≥ 25 y and ≥ 15 cig/day or ≥ 30 y and ≥10 cig/day	540 (27)	31 (1.5)	22 (1.1)
Santos et al.[15]	BRELT1	790	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	312 (39.5)	25 (3.1)	10 (1.3)
Hochhegger et al.[18]	BRELT2	3,470	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	218 (6.3)	122 (3.1)	74 (2.1)
Chiarantano et al.[81]	--	233	A 55-74 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y	38 (16.3)	3 (1.3)	3 (1.3)
Svartman et al.[82]	--	712	A 55-80 y; CS or FS (SF ≤ 15 y); and SH ≥ 30 p-y		-	11 (1.5)

LC: lung cancer; A: age; y: years; CS: current smoker; FS: former smoker; SF: smoke-free; cig/day: cigarettes/day; SH: smoking history; and p-y: pack-years. *CT-arm patients only. **Refers to tests considered positive according to the methodology used in each study. The disparity between the proportions is due to variations in the positivity criteria over the years and the number of rounds of tests carried out in each study.

The criteria for indicating LCS are summarized in Figure 1.

INCIDENTAL FINDINGS ON LDCT AND THEIR IMPLICATIONS

- Incidental findings on LDCT that are unrelated to LC are mostly irrelevant.
- When the incidental findings are relevant and interpreted correctly, they can improve the cost-effectiveness of the examination, as well as the quality of life and life expectancy of those screened.

Incidental findings (IFs) are those that are unrelated to LC but can be identified on screening with LDCT (Chart 1). Most IFs are clinically insignificant and do not need to be reported, others require referral to specialists and further evaluation, and some require immediate medical intervention.[88,89]

Relevant findings, when interpreted correctly, can increase the benefits and cost-effectiveness of screening. However, findings without clinical significance identified through screening programs can lead to unnecessary investigations and additional costs.[90-92]

The prevalence of IFs in the chest or adjacent regions (the neck and abdomen) differs significantly between screening programs, with rates ranging from 41% to 94%, and their incidence is higher in the first LDCT. In the NLST, the IFs most commonly identified were related to the cardiovascular system (8.5%), followed by the kidneys (2.4%), liver/biliary tract (2.1%), adrenal glands (1.2%), and thyroid (0.6%).[93]

Among the cases in which there are IFs, additional investigation, including the use of other imaging methods, is required in 9-15%.[90] Of all of the deaths in the LDCT arm of the NLST, 10% were due to diseases other than LC.[10]

In the NLST, overall mortality was 6.7% lower in the group undergoing LDCT.[10] Therefore, it is possible that there is an advantage to LDCT in that it can identify other diseases, such as cardiovascular diseases (coronary arteriosclerosis, aortic aneurysm, pericardial thickening, and calcifications), COPD (emphysema

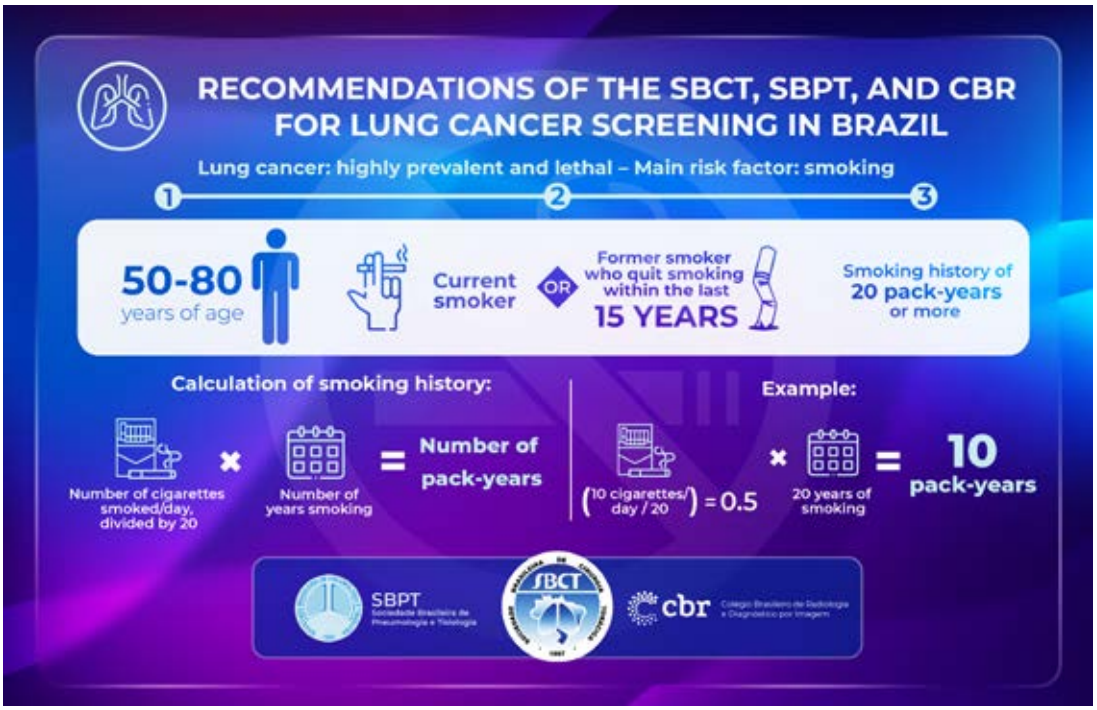

Figure 1. Eligibility criteria for lung cancer screening. SBCT: *Sociedade Brasileira de Cirurgia Torácica* (Brazilian Society of Thoracic Surgery); SBPT: *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Association); and CBR: *Colégio Brasileiro de Radiologia e Diagnóstico por Imagem* (Brazilian College of Radiology and Diagnostic Imaging).

and thickening of bronchial walls), and other diseases related or unrelated to smoking (e.g., interstitial lung lesions, sarcopenia, osteopenia, diaphragmatic hernias, neck cancer, and tracheal neoplasia).[88,94] The main IFs are described in Table 2.[91,92,94]

CHANGES CONSISTENT WITH GRANULOMATOUS LESIONS

- The high prevalence of granulomatous diseases in Brazil is a challenge for the implementation and cost-effectiveness of LCS in the country.
- The need for adjustments to the nodule management algorithms for use in the population of Brazil should be taken into consideration.
- Algorithm-based assessment and multidisciplinary management can reduce the rates of positivity, false-positives, and unnecessary procedures, as well as bringing our rates of invasive procedures closer to those reported for high-income countries.

Chief among the various challenges for implementing LCS programs in low- and middle-income countries is the high prevalence of granulomatous diseases, which could increase the proportion of false-positive results, consequently increasing the number of diagnostic/surgical procedures and associated complications.[15,22,95,96] In recent data, the incidence of tuberculosis in Brazil was 45 cases/100,000 population, significantly higher than the 2 cases/100,000 population reported for the United States.[97]

In a study of LCS conducted in South Korea—the Korean Lung Cancer Screening Project (K-LUCAS), which used the Lung CT Screening Reporting and Data System (Lung-RADS) version 1.0—the proportion of positive results was higher among the patients with evidence of tuberculosis sequelae than among those without (21% vs. 16%) and a reported history of tuberculosis was associated with a positive screening result.[96] The authors also reported that the specificity and accuracy of LCS were lower for patients with tuberculosis sequelae than for those without (80% for both vs. 85% for both, respectively), indicating that false-positive results are associated with a history of infection. In addition, they detected no association between tuberculosis sequelae and a diagnosis of neoplasia at screening.[96]

In the first round of screening in the BRELT1, the positivity rate was 39.5%, significantly higher than that reported for other screening programs.[15] Although the biopsy rate in the BRELT1 (3.1%) was comparable to those of the largest screening studies, it is still difficult to extrapolate these results to Brazil as a whole because of the great epidemiological heterogeneity in the country.[98]

To implement LCS with LDCT in Brazil, it is possible that adjustments in nodule management are needed in order to reduce the rates of positive and false-positive results, thereby reducing the number of unnecessary procedures.

In the BRELT2,[18] which involved more than 3,000 patients from various regions of Brazil, the patients in whom the findings were characteristic of residual granulomatous inflammation, findings classified as

Chart 1. Categories of incidental findings on low-dose CT.

Incidental findings	Category	Recommendation	Incidence
Mild/moderate CAC; COPD*; mild/moderate aortic dilation; emphysema; bronchial wall thickening; degenerative skeletal changes; cysts (hepatic, renal, pancreatic, or splenic); hiatal hernia; other diaphragmatic hernias; pleural plaques; minimal pulmonary fibrosis; bronchiectasis; adrenal lesions < 10 HU; low-risk thyroid nodules (< 1.5 cm)	Low clinical relevance	*A priori* investigation not recommended	50%
Marked CAC; mediastinal adenopathy > 1 cm; adrenal lesions > 10 HU; compression fractures; breast nodules; suspicious thyroid nodules; aortic aneurysm 4.0-5.5 cm	Possible clinical relevance	Recommended investigation	10%
Opacities suggestive of pneumonia; aortic aneurysm ≥ 5.5 cm; lobar or segmental atelectasis; lesion suspected of being cancer; large pleural or pericardial effusions	Clinically relevant	Recommended therapeutic intervention	< 1%

Adapted from Mazzone et al.[90,91] CAC: coronary artery calcification. *Depending on the stage of the disease.

Lung-RADS category 3 or 4, were followed clinically. That same trend of clinical follow-up was observed in the K-LUCAS protocol.[18,96] The authors of that study proposed a separate category to indicate lesions with a benign appearance that were classified as Lung-RADS category 3 or 4, considering a downgrade in the classification of these lesions from the baseline examinations. For example, noncalcified nodules measuring at least 8 mm, adjacent to scarring/calcified nodules, are to be reclassified to a new category—category 2b (b = benign). For category 2b, follow-up examinations would be still be annual, rather than every 3 months.[96] Given that the epidemiological situation of granulomatous diseases in Brazil is closer to that seen in South Korea than to that seen in high-income countries, a national screening program in Brazil could benefit from that adjustment.

DO PROBABILISTIC MODELS REDUCE THE NUMBER OF FALSE POSITIVES?

- Yes, prediction models can improve clinical interventions, population care development and resource optimization
- However, it is necessary to validate such models for use in heterogeneous populations and to define the cutoff score for practices related to the cancer risk.

The success of every LCS program is directly related to the assessment of the risk group, which can be complemented with prediction models. Prediction models can improve clinical interventions and the development of care for the population, as well as being ancillary tools for optimizing resources.

After the publication of the study conducted by Bach et al.,[99] research into risk prediction models for LC intensified.[100] Such probabilistic models, which were based on traditional variables, biomarkers, LDCT, and data exploration techniques, currently have good sensitivity and specificity. The most commonly used traditional variables are smoking intensity, occupational exposure to asbestos, the presence of emphysema, COPD, or pneumonia, and a family history of LC.[101]

The 2012 Prostatic, Lung, Colorectal and Ovarian Cancer Screening Model (PLCOm2012) was developed in smokers in the control arm of the PLCO study.[102] In comparison with the USPSTF criteria, the PLCOm2012 criteria include more personal factors (e.g., history of malignancy), a more detailed smoking history, family history, and the personal history of COPD.

The Lung Cancer Risk Assessment Tool risk model and Lung Cancer Death Risk Assessment Tool risk model were developed and validated in the control and chest X-ray arms of the PLCO study, respectively.[103,104]

Other LC risk models include the Kovalchik model, the Bach model, the Liverpool Lung Project model (and its simplified version), the Knoke model, the Hunt Lung Cancer model, and three two-stage clonal expansion models that predict the incidence of and death from LC.[105,106] Such models have included a variety of additional risk factors,[105,106] such as smoking intensity (cigarettes per day); occupational exposure to asbestos; emphysema, COPD, and pneumonia; and family history of LC.

The results are estimated by applying each risk model to previous cohorts, which serves as external validation. However, there is currently no consensus regarding the cutoff point that should be applied to LCS prediction models. In other words, the percentage of risk on which the recommendation for LCS should be based has not been defined.

In a systematic review of three different risk prediction models (a modified version of the PLCOm2012, the Lung Cancer Death Risk Assessment Tool model, and the Kovalchik model), estimation of outcomes in four different cohorts showed greater prevention of mortality in comparison with the risk factor-based criteria used by the NLST or USPSTF (2013 recommendations).[107]

Three of those studies demonstrated that screening efficiency (determined by the NNS) was better when

Chart 2. Incidental findings on low-dose CT.

Intrathoracic abnormalities

Cardiovascular

- They are common and cause more deaths than does LC. LDCT without ECG synchronization has a high false-negative rate.
- CAC: The identification of calcifications can help predict and reduce morbidity and mortality from cardiovascular diseases.
  - Standardization in the description and consensus regarding its diagnostic criteria and clinical significance are necessary.
  - The Society of Cardiovascular Computed Tomography and the Society of Thoracic Radiology confirm the combined use of LDCT in LCS and the CAC score as predictors of the risk of cardiovascular deaths in asymptomatic patients.
  - CAC scores by LDCT are applied through visual analysis.[b]
- Aortic aneurysm: Aortic dimensions increase with age and should be described in asymptomatic individuals.
  - At 70 years of age, the ascending and descending segments measure up to 3.5 cm and 2.7 cm, respectively.
  - Dilation becomes classified as an aneurysm when it is 50% greater than the normal diameter.
  - There is no recommendation to investigate aneurysms, unless there is a family history or associated genetic defect.
  - There are recommendations for annual or biennial monitoring of aneurysms, depending on their size, type, and location.
  - Aneurysm surgery (in the ascending or descending segment) is recommended if the diameter is ≥ 5.5 cm.[c]

COPD

- Individuals screened for LC are four times more likely to present changes suggestive of COPD (thickening of the bronchial walls, air trapping, hyperinflation, and emphysema) on LDCT.[a]
- Patients with COPD have a two to three times higher risk of developing LC.
- One third of individuals screened for LC have COPD, and its early detection can reduce morbidity and mortality.

Extrathoracic abnormalities[c]

Neck

- The *American College of Radiology* does not recommend further investigation for thyroid lesions ≤ 1.5 cm in patients > 35 years of age and without suspicious findings (invasion of adjacent structures or abnormal lymph nodes) and recommends ultrasonography for lesions > 1.5 cm or with findings suspicious for neoplasia.

Abdomen

- Liver: Changes are common, and most do not require additional investigation, especially lesions < 1.5 cm and findings suggestive of benignity (well-defined, homogeneous margins, and < 20 HU)
- Pancreas: Cystic lesions should be monitored by imaging.
- Gallbladder: Stones, calcifications, mural thickenings, distension, and polyps ≤ 6 mm do not require follow-up.
  - Ultrasonography is useful for evaluating polyps measuring 7-9 mm and indicating cholecystectomy for lesions ≥ 10 mm
- Spleen: Homogeneous lesions, with ≤ 20 HU and thin walls, do not require further investigation.
- Kidneys: Small, homogeneous lesions with a density of −10 to 20 HU or > 70 HU do not require further investigation.
  - MRI is recommended for lesions with a density of 21-69 HU, heterogeneous lesions or lesions with a density ≤ 10 HU with multiple calcifications or a calcification > 4 cm.
- Adrenal lesions < 1 cm, measuring 1-4 cm with < 10 HU, or that are stable for more than 1 year do not require additional testing; in other situations, it is recommended that other imaging methods (CT, MRI, or PET) be used.

LDCT: low-dose CT; CAC: coronary artery calcifications; LC: lung cancer; LCS: lung cancer screening; and ECG: electrocardiogram. [a]Based on Gierada et al.[94]. [b]Based on Kauczor et al.[92]. [c]Based on Mazzone et al.[90].

screening employed risk prediction models than when risk factor-based screening was used, whereas one study showed mixed results.[108]

A recent study of LCS in Brazil demonstrated that the yield of LDCT screening is lower in low-risk individuals than in high-risk individuals, the rates of positivity and LC detection being significantly lower in the former.[109] Therefore, screening low-risk patients could increase the number of LDCT examinations because of the lower diagnostic yield, resulting in increased costs compared with screening only the high-risk population. However, incorporating the PLCOm2012 with a 6-year LC risk ≥ 0.0151 as the eligibility criterion appears to increase the efficacy of LCS.[109] In that same study, the false-positive rate for the PLCOm2012 criteria was lower than was that for the NLST criteria, indicating a possible improvement in screening efficiency, even in a country with a high incidence of granulomatous diseases like Brazil.[109]

In general, the LC risk models are highly accurate, indicating that their use is viable for identifying high-risk populations. However, the model development process and the reports generated from the models are still not ideal, because they present a high risk of bias,

which limits their credibility and predictive accuracy, thus hindering their promotion and development.

MINIMUM REQUIREMENTS FOR LDCT

- Slice thickness ≤ 2.5 mm, preferably ≤ 1.0 mm
- Gantry rotation time of ≤ 500 ms
- Chest scanning time < 10 s
- Tube voltage of 100-120 kVp (for standard-sized patients)
- Tube current (mAs) preferably automatically modulated by the CT device
- Volumetric dose index of 3 mGy—effective radiation dose ≤ 1 mSv (for standard-sized patients)—the maximum radiation dose established for screening

Fundamental technical parameters for LCS using LDCT have been recommended by major international societies, especially the American College of Radiology (ACR) and the Society of Thoracic Radiology.[110]

The LDCT images should be acquired in scanners with at least 16 detector rows, with the helical technique and without intravenous administration of iodinated contrast. Obviously, the scan must cover the entire lungs, and it is extremely important that the patient performs a deep inspiration and adequate breath-hold, in order to guarantee the quality of the images, avoiding artifacts that could hinder the analysis of the examination.[110]

The slice thickness should be ≤ 2.5 mm, preferably ≤ 1.0 mm, and the gantry rotation time should be ≤ 500 ms. A chest scanning time of < 10 s is recommended.

For standard-sized patients (height, 170 cm; weight, 70 kg), the tube voltage should be set to 100-120 kVp, and the tube current (mAs), although it can be fixed, should preferably be modulated automatically by the CT scanner, which takes into account the physical characteristics of the patient, the tube voltage, and the table pitch (typically 0.7-1.5).

The maximum radiation dose established for LCS using LDCT corresponds to a volumetric dose index of 3 mGy—effective radiation dose ≤1 mSv—for a standard-sized patient, with appropriate dose reductions and increases for smaller and larger patients, respectively,[111] always following the premise that tomography should be performed with the lowest possible dose of radiation that guarantees a good quality diagnostic examination.

Suggested protocols for performing LDCT on a variety of devices from major manufacturers are available on the website maintained by the American Association of Physicists in Medicine.[74,75]

It is noteworthy that, in the wake of constant and important technological advances in the area, the most modern CT scanners currently available have features such as iterative reconstruction and deep learning, making it possible to obtain images of better quality (with less noise), even with greatly reduced radiation doses.

The radiation dose employed in LDCT is equivalent to approximately one-fifth of that of a "standard-dose" chest CT, and one-quarter of the average background radiation to which a person is exposed over the course of a year in the United States. The risk of radiation-induced malignancies in patients undergoing LCS with LDCT is considered low; greater attention should be paid to other risks such as false-positive results, overdiagnosis, and IFs without clinical relevance, which can prompt unnecessary additional interventions and generate anxiety in patients.[112]

After the examination has been performed, at least two image volumes should be reconstructed: one with a "standard" filter for evaluating soft tissues (including, for example, mediastinal structures); and another with a "lung" filter, which provides greater "spatial" (i.e., anatomical) resolution for evaluating the lung parenchyma, as well as for measuring and analyzing the contours of any nodules detected. Maximum intensity projections and multiplanar (coronal and sagittal) reconstructions are recommended for the detection and characterization of nodules, respectively.[113]

NODULE POSITIVITY CRITERIA: TWO-DIMENSIONAL MEASUREMENT VS. VOLUMETRY

- Potential gains when using volumetric measurement:
  - Greater reproducibility of measurements
  - Three-dimensional assessment of nodules
  - Increased sensitivity for assessing nodule growth
- Potential challenges when using volumetric measurement:
  - Difficulties in segmenting nodules adjacent to other lung structures
  - Difficulty in the assessment of subsolid nodules
  - Differences between measurements determined by different software
  - Variations according to CT reconstruction protocol
  - Issues related to equity in the availability of software throughout Brazil

Although several aspects, such as attenuation, shape, and location, should be considered when evaluating pulmonary nodules; size and growth are assumed to be the most important variables in estimating the probability of malignancy.[114] Regarding those two parameters, there are variations in nodule management algorithms in the screening protocols proposed to date, which differ in terms of positivity criteria and growth indicators. Therefore, the choice between linear measurements and volumetry is a sensitive point. For example, the NLST (conducted in the United States), as well as the BRELT1 and BRELT2 (both conducted in Brazil), used linear measurements in the assessment of solid nodules, whereas the NELSON trial primarily used volumetry, as have other European screening algorithms.[9,10,15,16,18]

The management protocol first suggested by the ACR—Lung-RADS, version 1.1—used linear measurements (specifically, calculating the mean nodule diameter to the first decimal place); however, volumetric notation was included as a possibility (ACR Lung-RADS 2019), a feature that was maintained in the latest version (ACR Lung-RADS 2022).[115,116]

The NELSON trial defined nodule growth as a 25% increase in the volume of a solid nodule or the solid component of a subsolid nodule, with subsequent stratification based on the volume doubling time (VDT), whereas the Lung-RADS defined it as an increase of 1.5 mm in the mean diameter or of 2 mm^3 in volume.[16,115-117]

The potential gains achieved by using volumetry rather than linear measurements include greater reproducibility of measurements, three-dimensional assessment of nodules, and increased sensitivity for assessing nodule growth, allowing, for example, the calculation of VDT, which would be a better parameter for determining their behavior.[118]

The use of linear measurements to measure solid nodules is associated with significant intraobserver and interobserver variability. In a study conducted by Revel et al.,[119] changes in size < 1.7 mm had only a 5% chance of representing a real change in the size of the nodules, an aspect that could have an impact not only on the categorization of nodules and the positivity rate but also on the definition of their growth.

In a study evaluating the categorization of solid nodules within the Lung-RADS criteria, interobserver agreement on the dimensions of nodules was found to be better when automated volumetric assessment was used than when automated or manual diameter measurement was used, and automated volumetric assessment was found to result in some nodules being reclassified to lower categories.[120]

Lung nodule volume is determined through semi-automated or automated analysis with specific software based on segmentation. It should be borne in mind that calculating the volume of nodules directly from their diameters leads to a significant overestimation of that volume. Heuvelmans et al.[121] showed that calculating the volume of nodules directly from their diameters (thus assuming sphericity) overestimated that volume, in comparison with semi-automated volume analysis, by approximately 47.2% when the mean diameter was used and by 85.1% when the maximum diameter was used.

Although there are advantages to the use of volumetry, it poses many challenges in clinical practice, including the following[118]: difficulties in segmenting nodules that are adjacent to other lung structures (e.g., pleural and vascular interfaces); difficulty in the evaluation of subsolid nodules; differences between measurements determined by the various types of software and the versions thereof; variations according to the CT reconstruction protocol (slice thickness, overlapping images, and different reconstruction algorithms); and, as one can imagine, issues related to equity in the availability of software throughout Brazil. Regarding variations in the measurements of nodule volume when different software is used, Zhao et al.,[122] for example, compared the performance of software from three different manufacturers, finding variations of up to 50% when comparing the measurements acquired.

Given the potential and challenges of volumetry, it would be acceptable for screening programs based on nodule diameter measurements to consider including a volume equivalent in their management algorithms.[91]

RISKS ASSOCIATED WITH LCS

- Radiation exposure—relatively low risk with LDCT
- Patient anxiety, unnecessary examinations/interventions, and poorer quality of life, due to the following:
  - False-positive results
  - Overdiagnosis
  - Irrelevant IFs
  - Incorrect decisions

Note: In relation to education and appropriate guidance on LCS, these risks can be minimized through the work of the multidisciplinary team and shared practice.

Prospective participants in an LCS program should be informed, through various means of communication but especially through a detailed explanation from their physician, about the benefits and potential risks of their participation.

Participation should be well documented, and written informed consent should be obtained before any procedure is performed. The authorization granted should extend to planned visits to carry out LDCT at regular intervals, as well as to the use of data, including the description of health status, test results, and reports of adverse effects, in subsequent studies.[123]

The following are the main risks related to LCS with LDCT:

Radiation exposure—Irradiation associated with one LDCT scan ranges from 0.65 mSv to 2.36 mSv, and the cumulative exposure over 25 years of annual screening would be 20.8-32.5 mSv. For example, the mean irradiation during a PET/CT scan is 4 mSv. To date, there have been no studies estimating the overall risk of cancer in general or of fatal cancer induced by irradiation in annual screening up to 80 years of age.[74,75]

False-positive results—Any result that leads to additional investigation and which does not result in a diagnosis of cancer is considered a false-positive. The false-positive rate depends on a series of confounding factors, such as the nodule size considered positive, the use of VDT, and the characteristics of the nodule to be considered in each study. In cohort studies, the reported proportion of false positives ranges from 9.6% to 49.3% at baseline (prevalent round), and that rate decreases with each additional round of screening

(incident rounds), with a variation of 5.0-28.6%.[74,75] The false-positive rate in the baseline examination has been shown to be lower when a structured CT reading instrument with the Lung-RADS method is used than when the NSLT reading method is used (12.8% vs. 26.0%).[124]

The worst harm caused by a false-positive result is that it creates a need for diagnostic clarification, with or without invasive procedures.[74,75]

In a study involving 3,280 patients selected for LCS, 342 (10%) had category 4 findings according to the Lung-RADS reading. Of those, 100 (approximately 30%) were found to have LC, the vast majority diagnosed at an early stage, when the disease is potentially curable. That represents a 3% yield, and only 15 patients (0.45%) underwent some type of surgical procedure in which the result did not confirm cancer, with practically no morbidity and zero mortality.[125]

- Overdiagnosis—Overdiagnosis can be defined as the detection of cancer that would not have become clinically significant during the lifetime of the patient. The overdiagnosis rate ranges from 0% to 67%.[74,75] In a meta-analysis, it was observed that there is a significant increase in overdiagnosis during the follow-up period.[126]
- Psychological risk—Although participating in LDCT screening has not been found to worsen quality of life or anxiety over 2 years of follow-up, a significant increase in distress and anguish has been observed, especially in cases with indeterminate results.[127,128] The understanding that an early-stage cancer could be discovered during screening has served to overcome fears of undergoing an unnecessary procedure.[74,75,127,128]
- IFs—The rate of IFs varies greatly, depending on the definition of what is considered an IF and on the mean age of the study participants.[74,75,129] Although the detection of some IFs can cause distress, it can improve the diagnosis and early management of potentially serious diseases.

The risks of LCS are relatively low and can be reduced with a quality diagnostic assessment, practices based on valid algorithms, and the involvement of a multidisciplinary team.

MINIMUM STRUCTURE AND THE ROLE OF A MULTIDISCIPLINARY TEAM

- Screening centers
  - Multidisciplinary team for recruiting, as well as for the acquisition and interpretation of radiological images, with the ability to carry out the differential diagnosis in cases with positive results and appropriate treatment in cases of cancer
- Minimal structure
  - Access to a smoking cessation program
  - Radiology clinic with LDCT (low voltage, 16 channels)
  - Specialized team and standardized (Lung-RADS) description in reports
  - Access to PET/CT for diagnosis and preoperative staging
  - Interventional radiology and bronchoscopy to perform biopsies
  - Surgical center with the capability to perform thoracotomy and video-assisted surgery
  - Structure for patient navigation

An LCS program is established on a population basis and therefore requires an articulated organizational structure to reconcile two important aspects:

- It should be offered in the form of a large cohort with universal distribution, and there should therefore be centers that are close to the places of residence of the participants.
- There should be local or regional screening centers with multidisciplinary teams for recruiting, as well as for the acquisition and interpretation of radiological images, with the ability to carry out the differential diagnosis in cases with positive results and to provide appropriate treatment in cases of cancer.[123]

It is known that the cost-effectiveness of LCS increases when it is applied in conjunction with a smoking cessation program, and a program structured for that purpose should therefore be part of the minimum structure.[130,131]

Local and regional centers must be certified, authorized, and accredited by a national organization. The minimum structure for an LCS center should include a radiology clinic with a 16-channel CT scanner (although it is possible with a 4-channel CT scanner, as was used in the NSLT), whenever possible with a computerized program for volumetric reading of the lesion, the ability to describe the results in a standardized way using the Lung-RADS system, and a quality control sector. The centers should have access to PET/CT for diagnostic follow-up of suspicious nodules and preoperative staging.

Another crucial point is the capacity to perform biopsy, which can be guided by CT, or another minimally invasive surgical procedure, preferably with preoperative markup in the case of lesions that are invisible or nonpalpable. Although an interventional pulmonology clinic with endobronchial bronchoscopy is desirable, the economic conditions of each center must be taken into account so as not to make the program unfeasible. The surgical center should be structured to allow thoracotomy and video-assisted thoracoscopic surgery to be performed.

Finally, the LCS center should have a professional structure to help patients navigate the program, guiding them through invasive investigation and periodic examinations of the lesions identified or referring them to the smoking cessation program.

The administrative structure of each center should have the capacity to record all data and results in order to store and report all information to the national screening center. Of equal importance is sector planning to promote continued training for the entire team.[132,133]

Interaction between the primary care clinician and the thoracic surgeon, pulmonologist, or both, as well as between them and the radiologist, pathologist,

oncologist, and radiotherapist, is of fundamental importance for the success of the screening program. No less important is the participation of the nursing and social assistance sectors.

All of the professionals should be subject to regional or central administrative medical authority that is responsible for communication at different levels and a referral and counter-referral system, as well as for storing data and images to be consulted over time.[22,123] Test results should be communicated to participants in written form and orally, the impact of the result being weighed for each individual.[132] Everyone on the multidisciplinary team should have a clear understanding of their role, be familiar with the brief guidelines on smoking cessation, and know how to recommend facilities for intensive treatment.[134,135]

At LCS centers, decisions should be made jointly and should be based on the six pillars of quality health care, which are safety, effectiveness, efficiency, timeliness, equity, and patient-centeredness. Adherence to LCS is not high and could be improved through clear discussion about the advantages and potential risks of screening and not screening.[136] In addition, continuity of care must be guaranteed when a participant moves from one setting to another, and information about their goals, beliefs, and values, as well as their current clinical status, should always be reported in order to avoid misunderstandings.[134]

Ensuring the benefits of an LCS program requires an organized structure, trained staff, and appropriate equipment, concentrated at LCS centers.[123]

POST-LDCT MANAGEMENT ALGORITHM—LUNG-RADS

In 2014, the ACR developed the Lung-RADS, which was modeled on the success of its Breast Imaging Reporting and Data System.[116]

The Lung-RADS allows uniform reporting and management of abnormal findings on LDCT examinations in LCS and aims to facilitate successful implementation in radiology practice outside the scope of clinical trials.[116] The Lung-RADS is also an essential part of quality assurance and screening log reports. The latest Lung-RADS version, released by the ACR in 2022, was based on evidence collected in previous years,[116] as detailed in Tables 3 and 4.

The Lung-RADS Committee is made up of 8 of the most prominent experts in the field, who carry out studies of the existing literature and publish periodic updates. We believe that using the Lung-RADS recommendations is the way to make the most accurate decisions after LDCT in an LCS program.

COST-BENEFIT ANALYSIS OF SCREENING

- LCS with LDCT is probably cost-effective, and its cost-benefit ratio, despite involving multiple factors, also tends to be adequate.

Cost-benefit analysis is one of the most important aspects of public health policies. When evaluating screening, for benign and malignant diseases alike, it is necessary to demonstrate its advantages in relation to its costs, especially for the funding sources.[137]

In relation to LCS, it is expected that there will be a high number of LDCT examinations for each patient diagnosed and treated, which increases the overall cost of the program. Cost-effectiveness, as well as the benefit of reducing mortality and increasing early diagnosis, should be clearly demonstrated.[137-139]

It is also necessary to understand the difference between a cost-effectiveness analysis, which considers the cost of the program only for the examination and the determined outcome, and a cost-benefit analysis, which also takes into account other benefits, such as smoking cessation.[137,138]

The cost-effectiveness analysis model that comes closest to reality is the ***MI****crosimulation* ***SC****reening* ***An****alysis-Lung* (MISCAN-Lung), which uses a semi-Markov model to simulate the appearance of neoplasms at the population scale.[139] A study conducted in Canada showed that, according to the MISCAN-Lung model, LCS is cost-effective for high-risk populations and that the cost decreases as smoking history in pack-years increases, although the number of life-years gained does not increase.[139]

To analyze the cost-benefit of screening, the cost-effectiveness relationship was initially assessed in a systematic review that included 45 studies and employed a ***P****atients of interest,* ***I****ntervention to be studied,* ***C****omparison of interventions, and* ***O****utcome of interest* (PICO) type of strategy, as follows[140]: patients/population of interest—smokers (or former smokers) between 55 and 79 years of age with a smoking history > 20 pack-years; intervention—LDCT; comparison—chest X-ray or no screening; and outcome of interest—cost-effectiveness of screening with LDCT.

In that study,[140] it was clear that annual screening with LDCT is cost-effective for the desired population, and the cost-effectiveness ratio is even greater for biennial screening, although the roles of risk prediction models and smoking cessation interventions were unclear.

Another systematic review corroborated the cost-effectiveness findings and suggested that such screening programs should be implemented even in situations of limited financial resources and even if LDCT has to be performed at a lower (biennial) frequency.[141] However, that review does not necessarily reflect the reality in Brazil.

A study carried out in China, an upper-middle-income country with a high prevalence of granulomatous diseases and whose indicators are comparable to those of in Brazil, showed, using the Markov model, that screening with LDCT for patients over 60 years of age cost US$113.88 million but was cost-effective, reducing LC-related deaths by 16.1%.[142]

Chart 3. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 1).

Category		Description	Management
0	Incomplete data (estimated population prevalence: ≈ 1%)	Localized anterior chest CT examination for comparison (see Note 1)	Comparison with previous chest CT
		Part or all of the lungs cannot be evaluated	Additional LDCT required for LCS
		Findings suggestive of an inflammatory or infectious process (see Note 2)	LDCT in 1-3 months
1	Negative (estimated population prevalence: 39%)	No pulmonary nodules OR nodule with benign characteristics • Complete, central, popcorn-shaped, concentric ring or fat-containing calcifications	LDCT screening every 12 months
2	Benign Based on image features or indolent behavior (estimated population prevalence: 45%)	Juxtapleural nodule • Mean diameter < 10 mm (524 mm^3) at baseline or new AND • Solid nodule; smooth margins; oval, lentiform, or triangular shape Solid nodule • < 6 mm (< 113 mm^3) at baseline OR • New nodule < 4 mm (< 34 mm^3) Subsolid nodule • < 6 mm mean total diameter (< 113 mm^3) at baseline Non-solid nodule • < 30 mm (< 14,137 mm^3) at baseline, new or growing OR • ≥ 30 mm (≥ 14,137 mm^3) stable or growing slowly (see Note 3) Airway nodule, subsegmental at baseline, new or stable (see Note 4) Category 3 nodules that are stable or decreased in size on 6-month follow-up CT OR Category 3 or 4A nodules that disappear on follow-up OR Category 4B findings proven to be of benign etiology upon diagnostic evaluation Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm^3) with a solid component < 6 mm (< 113 mm^3 at baseline • OR • New nodule < 6 mm mean total diameter (< 113 mm^3) Non-solid nodule • ≥ 30 mm (≥ 14.137 mm ^{3}) at baseline or new Atypical lung cyst (see Note 5) • Enlarging cystic component (mean diameter) of a thick-walled cyst Category 4A nodule that is stable or has decreased in size at 3 months of CT follow-up (excluding airway nodules)	

Modified from American College of Radiology Committee on Lung-RADS.[116]
Lung-RADS: Lung CT Screening Reporting and Data System; LDCT: low-dose CT; and LCS: lung cancer screening.
Notes:
1. Previous examinations: If waiting for previous examinations (either a pre-screening test or CT), Lung-RADS Category 0 is temporary until the comparison study is available and a new Lung-RADS Category is determined.
2. Suspected infectious or inflammatory disease:
a. In the case of Lung-RADS 0 with 1-3 months of follow-up, LDCT may be recommended on the basis of pulmonary findings, suggesting an undetermined infectious or inflammatory process. Such findings may include segmental or lobar consolidation, multiple (> 6) new nodules, large (> 8 mm) solid nodules appearing within a small interval, and new nodules in certain clinical settings (e.g., immunocompromise). At 1-3 months of follow-up, a new management recommendation and Lung-RADS classification should be provided based on the most suspicious nodules.
b. New solid or subsolid nodules with imaging features more concerning for malignancy than an inflammatory or infectious process, with the Lung-RADS 4B size criteria may be classified as such provided they have the appropriate clinical diagnosis/evaluation.
3. Slow-growing solid or ground-glass nodules: A ground-glass pattern nodule that demonstrates growth on multiple screening tests but does not meet the size increase threshold of > 1.5 mm for any 12-month interval may be classified as Lung-RADS 2 until the nodule meets criteria for another category, such as development of a solid component (after which the case should be managed according to the solid nodule criteria, on a per-patient basis).

Chart 4. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 2).

Category		Description	Management
3	Probably benign Based on imaging features (estimated population prevalence: 9%)	Solid nodule • ≥ 6 to < 8 mm (≥ 113 to < 268 mm³) OR • New 4 mm to < 6 mm (34 to < 113 mm³) Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm³) with solid component < 6 mm (< 113 mm³ at baseline OR • New < 6 mm mean total diameter (< 113 mm³) Non-solid nodule • ≥ 30 mm (≥ 14.137 mm³) at baseline or new Atypical lung cyst (see Note 5) • Enlarging cystic component (mean diameter) of a thick-walled cyst Category 4A nodule that is stable or has decreased in size at 3 months of CT follow-up (excluding airway nodules)	New LDCT at 6 months
4A	Suspicious (estimated population prevalence: 4%)	Solid nodule • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm³) at baseline OR • Growth < 8 mm (< 268 mm³) OR • New 6 to < 8 mm (113 to < 268 mm³) Subsolid nodule • ≥ 6 mm mean total diameter (≥ 113 mm) with solid component of ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm ³) at baseline OR • New or growing solid component < 4 mm (< 34 mm³) Nodule in the airways Segmental or more proximal at baseline or new (see Note 4) Atypical lung cyst (see Note 5) • Thick-walled cyst OR • Multilocular cyst (at baseline) OR • Thin- or thick-walled cyst that becomes multilocular	New LDCT at 3 months PET/CT may be considered if there is a nodule or solid component ≥ 8 mm (≥ 268 mm³)
4B	Very suspicious (estimated population prevalence: 2%)	Nodule in the airways Segmental or more proximal, and stable or growing (see Note 4) Solid nodule • ≥ 15 mm (≥ 1,767 mm ³) at baseline OR • New or growing ≥ 8 mm ³ (≥ 268 mm ³) Subsolid nodule • Solid component ≥ 8 mm (≥ 268 mm³) at baseline OR • New or growing solid component ≥ 4 mm (≥ 34 mm³) Atypical lung cyst (see Note 5) • Thick-walled cyst with increasing thickness/nodularity OR • Multilocular cyst growth (mean diameter) OR • Multilocular cyst (with increased loculation or new/increased opacity (nodular, ground glass, or consolidation) Solid or subsolid nodule that demonstrates growth on multiple screening examinations	Referral for future clinical evaluation Diagnostic chest CT, with or without contrast PET/CT may be considered if there are nodules or solid components ≥ 8 mm (≥ 268 m³); removal of tissue samples; or referral for further clinical assessment Management depends on clinical assessment, patient preference and likelihood of malignancy (see Note 6)
4X	(estimated population prevalence: < 1%)	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion of lung cancer	

Continue...▶

Chart 4. Lung CT Screening Reporting and Data System, version 2022: classification and recommendations for lung nodule management during lung cancer screening (part 2). (Continued...)

Category		Description	Management
S	Significant or potentially significant (estimated population prevalence: 10%)	Modifier: May add to category 0-4 for clinically significant or potentially clinically significant non-lung cancer findings	According to the specific finding

Modified from American College of Radiology Committee on Lung-RADS.[116]
Lung-RADS: Lung CT Screening Reporting and Data System; LDCT: low-dose CT.
Notes:
4. Nodules in the airways
a. Endobronchial or endotracheal abnormalities that are segmented or more proximal are classified as Lung-RADS 4A
b. Segmental abnormalities or multiple tubular abnormalities favor an infectious process. If no underlying obstructive nodules are found, these findings can be classified as Lung-RADS 0 (probably infectious or inflammatory) or 2 (benign).
c. The presence of air in segmental or more proximal airway abnormalities generally favors secretions. If no underlying soft tissue nodule is identified, these findings can be classified as Lung-RADS 2.
d. Segmental or more proximal airway nodules that are stable or enlarging at 3 months of CT follow-up are upgraded to Lung-RADS 4B with management recommendations for future clinical evaluations (typically bronchoscopy).
5. Atypical lung cysts
a. Thin-walled cysts—unilocular cysts with a uniform thickness < 2 mm. Thin-walled cysts are considered benign and are not classified or managed by Lung-RADS.
b. Thick-walled cysts—unilocular with uniform thick wall, asymmetric wall thickening, or nodular wall thickening ≥ 2 mm (cystic component is the dominant feature); manage as an atypical pulmonary cyst.
c. Multilocular cyst—thin- or thick-walled cyst with internal separations; manage as an atypical pulmonary cyst.
d. Cavitary nodule—wall thickening is the dominant feature; manage as a solid nodule (mean total diameter).
e. Cyst with associated nodule: any cyst with a nodule (solid, subsolid, or ground glass); management is based on Lung-RADS criteria for resources of most concern.
f. Growth—> 15 mm increase in nodule size (mean diameter), wall thickness, and/or cystic component size (mean diameter) occurring within a 12-month interval.
g. Fluid-containing cysts may represent an infectious process and are not classified in Lung-RADS unless other features of concern are identified.
h. Multiple cysts may indicate an alternative diagnosis such as Langerhans cell histiocytosis or lymphangioleiomyomatosis if they are not classified on the Lung-RADS unless other worrisome features are identified.
6. Category 4B
Management is impaired based on clinical assessment (comorbidities), patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al.[159] assessment tool when making recommendations.

To arrive at the cost-benefit ratio based on cost-effectiveness, we should consider, in addition to the cost-effectiveness ratio of LDCT in relation to LC-related mortality, the following aspects[4,137,143,144]:

1. Treating early-stage disease is potentially less costly than is treating advanced-stage disease and has better outcomes. Screening will likely increase the number of individuals diagnosed at an early stage.
2. Screening ends up changing the staging of LC that would be diagnosed late, as observed in the IELCAP study.[144]
3. There are costs associated with ancillary tests, such as biopsies.
4. The treated patient, even if still asymptomatic, tends to return to work more quickly, thus reducing the socioeconomic impact of the disease.
5. There is an increase in the number of hospitalizations due to factors associated with advanced-stage disease, such as dyspnea, thromboembolism, and intractable pain, which increases costs.
6. The screening program should be associated with the smoking history, which in itself leads to the prevention of other diseases and therefore to a cost reduction.
7. The cost of LDCT is low (approximately US$250 in the United States in 2023), and its availability has increased, even in low- and middle-income countries.
8. LDCT examinations end up diagnosing diseases other than LC, which can be treated in a timely manner. Their diagnosis and treatment increase the program costs but tend to reduce overall nonspecific mortality.

The analysis considering such factors is complex, and no predictive model can accurately estimate the costs. There are estimates for the United States, although with divergent values, depending on health insurance and other factors.[137] Nevertheless, there is agreement on the possibility of a good cost-benefit ratio for the at-risk population.[145] Although there is a lack of data on cost-effectiveness and cost-benefit in Brazil, it is possible to assume, by interpreting the results of international studies, that LCS will produce similar results in the country.

After that analysis, it can be concluded that LCS with LDCT is probably cost-effective, and its cost-benefit ratio, despite involving multiple factors, also tends to be adequate. Although data from Brazil are needed in order to validate these models, this is an open field that is of great interest, especially to patients who

would benefit from early diagnosis and treatment, with reduced mortality.

SCREENING PERSPECTIVES (NEW MARKERS)

- New markers are promising, although their efficacy is still under evaluation and their costs are high.
- The use of molecular or protein-based tumor biomarkers, bronchoscopy with autofluorescence, DNA methylation, exhaled breath, circulating free DNA, microRNA, metabolomics, and the combination of images (deep learning) with biomarkers are being studied.

In recent years, new LCS modalities have been investigated. The main unmet clinical needs are risk refinement to improve the selection of individuals undergoing screening and the characterization of indeterminate nodules found during LDCT-based screening.

In the NLST, blood, urine, and sputum samples from more than 10,000 participants were stored for later analysis.[146,147] However, there are as yet no molecular or protein-based tumor biomarkers that can be used efficiently and implemented reliably in a screening program.[92]

Autofluorescence bronchoscopy has greater sensitivity for detecting precancerous lesions of the bronchial mucosa than does conventional bronchoscopy. However, the results of most previous studies do not support its use as an LCS tool.[148]

Some studies have pointed to DNA methylation as one of the key factors in the progression of LC. Recent studies have been performed on tumor tissue; findings in blood and other samples showed lower sensitivity and specificity.[149] Another study found that, for five of the six genes evaluated (*SOX17*, *TAC1*, *HOXA7*, *CDO1*, *HOXA9*, and *ZFP42*), DNA methylation in plasma and sputum was more common in patients with LC than in control patients ($p < 0.001$).[150]

It is possible to detect volatile fragments of cells and DNA in exhaled breath condensate. Some studies have suggested that this matrix can be used in order to differentiate between benign and malignant nodules, as well as to predict the treatment response and recurrence. Studies for training in and validation of the use of a portable electronic nose for LCS have found it to have a diagnostic accuracy of 83%. These findings suggest that exhaled breath is a valid marker of LC and could be useful for triage.[151,152]

Circulating free DNA appears to be more suitable for identifying mutations in the driver gene in patients with known neoplasia than for making an early diagnosis. Initial studies have shown that it does not predict the risk of LC but does predict perioperative survival. However, a retrospective analysis of microRNAs showed their potential to increase the specificity of LDCT, with a notable (five-time) reduction in the false-positive rate.[153] In combination with LDCT findings, microRNA can help stratify the risk of LC. That risk stratification is now being tested prospectively in a screening trial involving more than 4,000 people.[154,155]

Changes in LC metabolites (metabolomics: changes in glycolysis, citric acid cycle, amino acid metabolism, and cell membrane synthesis) provide a direct functional reading of phenotypic changes associated with the development of lung tumors and can help differentiate between histological subtypes or target mutations.[156]

Combining image-based deep learning with biomarkers can be an effective means of characterizing lung nodules. Radiomics analysis is capable of identifying *EGFR* and *KRAS* mutations, as well as of predicting survival. Some studies have shown that integrating biomarkers and radiological characteristics is a good method for predicting LC. The use of integrated models has been shown to be superior to that of serum biomarkers in isolation and represents a quite promising approach for the future of early LC detection, especially if artificial intelligence is incorporated.[147]

The scientific community is also awaiting the results of the Circulating Cell-Free Genome Atlas study for the early detection of cancer. In that study, plasma samples collected during a 5-year follow-up period will be analyzed by whole genome sequencing and integrated with patient clinical information.[157,158]

All of these tools could be of great importance for the future of screening. However, the high cost of developing and implementing them could hinder their incorporation into clinical practice in population-based health care.

FINAL CONSIDERATIONS

Early detection of LC is essential for improving clinical outcomes. The approach to the vulnerable population, especially smokers, should be carried out in a multidisciplinary manner, with the help and participation of public authorities, community health agents, family members, and patient support organizations.

In this document, experts from three of the main medical societies dedicated to the treatment of chest diseases (the SBPT, SBCT, and CBR) came together to form the study group, aiming to formulate the first LCS recommendations for Brazil, and this is a first step toward discussions on the topic, which is of great importance.

In Figure 2, we present an infographic summarizing the main points of these recommendations.

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AUTHOR CONTRIBUTIONS

All of the authors participated in one or more phases of the drafting of this consensus: 1) study conception

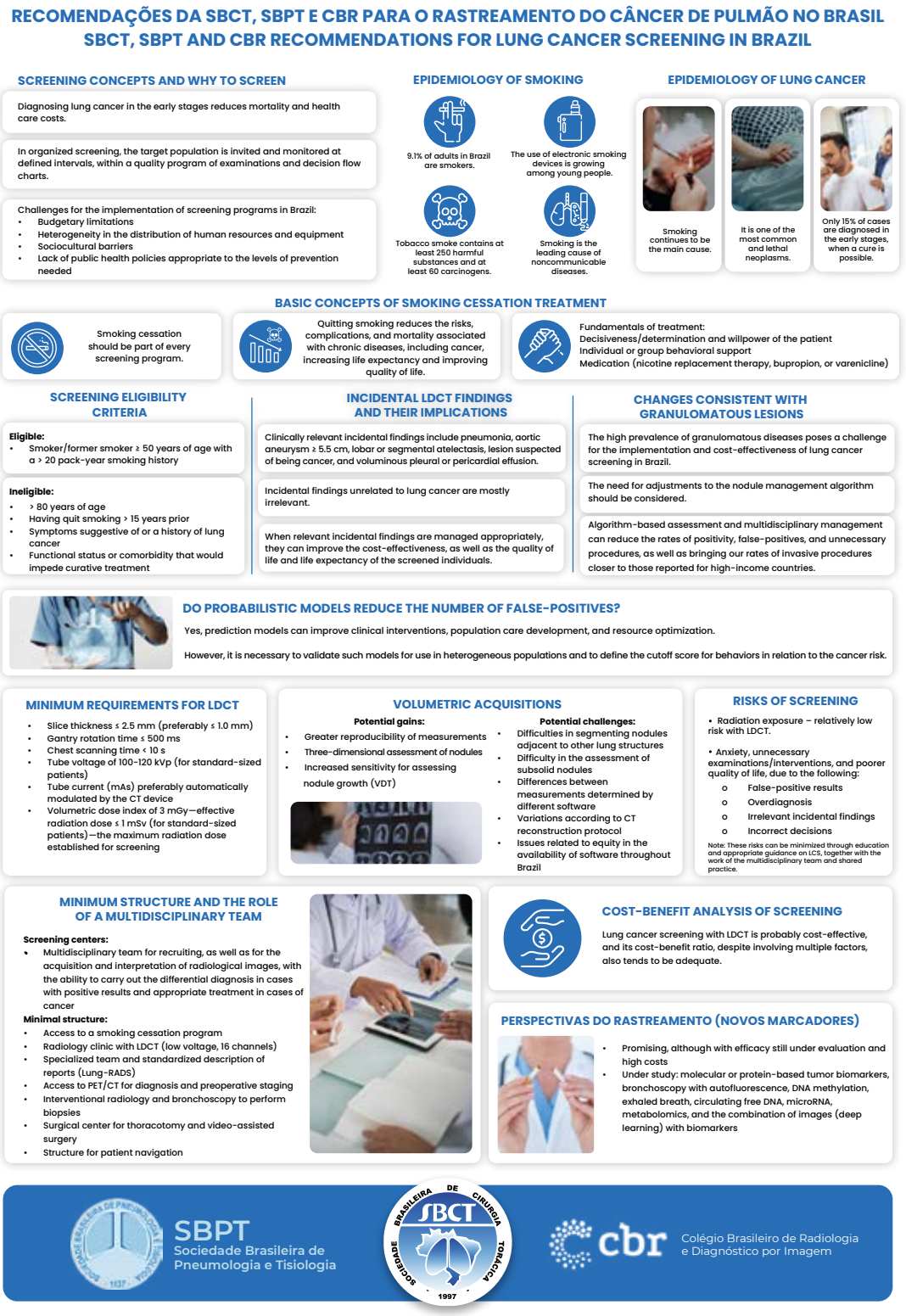

Figure 2. Summary of the main points of recommendations for lung cancer screening in Brazil. LDCT: low-dose CT; VDT: volume doubling time; and Lung-RADS: Lung CT Screening Reporting and Data System.

and planning, as well as interpretation of evidence; 2) drafting and revision of the preliminary and final versions of the manuscript; and 3) approval of the final version of the manuscript. The final version was

prepared by LFFP, RSS, DOB, and JF, after agreement by all members of the working group.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Global Burden of Disease 2019 Cancer Collaboration; Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, et al. Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life Years for 29 Cancer Groups From 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol. 2022;8(3):420-444. https://doi.org/10.1001/jamaoncol.2021.6987
2. Santos MO. Estimativa 2018: Incidência de Câncer no Brasil. Rev Bras Cancerol. 2018;64(1):119-120. https://doi.org/10.32635/2176-9745.RBC.2018v64n1.115
3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. https://doi.org/10.3322/caac.21708
4. Guzman R, Guirao À, Vela E, Clèries M, García-Altés A, Sagarra J, et al. Outcomes and cost of lung cancer patients treated surgically or medically in Catalunya: cost-benefit implications for lung cancer screening programs. Eur J Cancer Prev. 2020;29(6):486-492. https://doi.org/10.1097/CEJ.0000000000000566
5. Brasil. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. [homepage on the Internet]. Rio de Janeiro: INCA, 2021. [cited 2023 May 25]. Detecção precoce do câncer. [Adobe Acrobat document, 74p.]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/deteccao-precoce-do-cancer.pdf
6. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA. 2011;306(17):1865-1873. https://doi.org/10.1001/jama.2011.1591
7. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. The Lancet. 1999;354(9173):99-105. https://doi.org/10.1016/S0140-6736(99)06093-6
8. Henschke CI, Boffetta P, Yankelevitz DF, Altorki N. Computed tomography screening: the international early lung cancer action program experience. Thorac Surg Clin. 2015;25(2):129-143. https://doi.org/10.1016/j.thorsurg.2014.12.001
9. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. https://doi.org/10.1056/NEJMoa1102873
10. National Lung Screening Trial Research Team. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. J Thorac Oncol. 2019;14(10):1732-1742. https://doi.org/10.1016/j.jtho.2019.05.044
11. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med. 2016;193(5):542-551. https://doi.org/10.1164/rccm.201505-1040OC
12. Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening-Results from the randomized German LUSI trial. Int J Cancer. 2020;146(6):1503-1513. https://doi.org/10.1002/ijc.32486
13. Paci E, Puliti D, Lopes Pegna A, Carrozzi L, Picozzi G, Falaschi F, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax. 2017;72(9):825-831. https://doi.org/10.1136/thoraxjnl-2016-209825
14. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. Am J Respir Crit Care Med. 2015;191(10):1166-1175. https://doi.org/10.1164/rccm.201408-1475OC
15. dos Santos RS, Franceschini JP, Chate RC, Ghefter MC, Kay F, Trajano AL, et al. Do Current Lung Cancer Screening Guidelines Apply for Populations with High Prevalence of Granulomatous Disease? Results From the First Brazilian Lung Cancer Screening Trial (BRELT1). Ann Thorac Surg. 2016;101(2):481-488. https://doi.org/10.1016/j.athoracsur.2015.07.013
16. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-513. https://doi.org/10.1056/NEJMoa1911793
17. Sadate A, Occean BV, Beregi JP, Hamard A, Addala T, de Forges H, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. Eur J Cancer Oxf Engl 2020;134:107-114. https://doi.org/10.1016/j.ejca.2020.04.035
18. Hochhegger B, Camargo S, da Silva Teles GB, Chate RC, Szarf G, Guimarães MD, et al. Challenges of Implementing Lung Cancer Screening in a Developing Country: Results of the Second Brazilian Early Lung Cancer Screening Trial (BRELT2). JCO Glob Oncol. 2022.8:e2100257. https://doi.org/10.1200/GO.21.00257
19. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. Nat Rev Clin Oncol. 2021;18(3):135-151. https://doi.org/10.1038/s41571-020-00432-6
20. Adams SJ, Stone E, Baldwin DR, Vliegenthart R, Lee P, Fintelmann FJ. Lung cancer screening. Lancet. 2023;401(10374):390-408. https://doi.org/10.1016/S0140-6736(22)01694-4
21. Yang SC, Wang JD, Wang SY. Considering lead-time bias in evaluating the effectiveness of lung cancer screening with real-world data. Sci Rep. 2021;11(1):12180. https://doi.org/10.1038/s41598-021-91852-6
22. Raez LE, Nogueira A, Santos ES, Dos Santos RS, Franceschini J, Ron DA, et al. Challenges in lung cancer screening in Latin America. J Glob Oncol. 2018;4:1-10. https://doi.org/10.1200/JGO.17.00040
23. Edelman SE, Guerra RB, Edelman SM, Lopes da Silva L, Aleixo GFP, Matuda RMK, et al. The challenges of implementing low-dose computed tomography for lung cancer screening in low- and middle-income countries. Nat Cancer. 2020;1(12):1140–52. https://doi.org/10.1038/s43018-020-00142-z
24. Warren GW, Alberg AJ, Kraft AS, Cummings KM. The 2014 Surgeon General's report: "The health consequences of smoking–50 years of progress": a paradigm shift in cancer care. Cancer. 120(13):1914-1916. https://doi.org/10.1002/cncr.28695
25. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
26. Almeida A. Tipos e formas mais comuns de consumo de nicotina: tabaco sem fumaça. Em: Tabagismo: prevenção e tratamento. 1st ed. Rio de Janeiro, RJ: DiLivros Editora; 2021. p. 29-34.
27. Viegas CAA. Tipos e formas mais comuns de consumo de nicotina: tabaco com fumaça. Em: Tabagismo: prevenção e tratamento. 1st ed. Rio de Janeiro, RJ: DiLivros Editora; 2021. p. 35-39.
28. Martins S. Tipos e formas mais comuns de consumo de nicotina: dispositivos eletrônicos para fumar. Em: Tabagismo: prevenção e tratamento. 1st ed. Rio de Janeiro, RJ: DiLivros Editora; 2021. p. 40-48.
29. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General [monograph on the Internet]. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016. [cited 2023 May 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538680/
30. Lyzwinski LN, Naslund JA, Miller CJ, Eisenberg MJ. Global youth vaping and respiratory health: epidemiology, interventions, and policies. Npj Prim Care Respir Med. 2022;32(1):14. https://doi.org/10.1038/s41533-022-00277-9
31. Bertoni N, Szklo AS. Electronic nicotine delivery systems in Brazilian state capitals: prevalence, profile of use, and implications for the National Tobacco Control Policy [Article in Portuguese]. Cad Saude Publica. 2021;37(7): e00261920. https://doi.org/10.1590/0102-311X00261920
32. Martins S, Araújo AJ, Wehrmeister FC, Freitas BM, Basso RG, Santana ANC, et al. Prevalence and associated factors of experimentation with and current use of water pipes and electronic cigarettes among medical students: a multicentric study in Brazil. J. Brasil Pneumol. 49(1):e20210467. https://doi.org/ 10.36416/1806-3756/e20210467
33. Corrêa PCRP. No controversy: e-cigarettes are not a treatment for tobacco/nicotine cessation. J Bras Pneumol. 2022;48(5):e20220283. https://doi.org/10.36416/1806-3756/e20220283
34. IBGE. [homepage on the Internet] Rio de Janeiro, RJ: IBGE; c2020 [cited 2023 Jun 20]. PESQUISA NACIONAL DE SAÚDE 2019: PERCEPÇÃO DO ESTADO DE SAÚDE, ESTILOS DE VIDA,

DOENÇAS CRÔNICAS E SAÚDE BUCAL: Brasil e Grandes Regiões. [Adobe Acrobat document, 113p.]. Available from: https://biblioteca.ibge.gov.br/visualizacao/livros/liv101764.pdf

35. Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. Prev Med. 2014;69:248-260. https://doi.org/10.1016/j.ypmed.2014.10.009
36. Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography–High-Resolution Mass Spectrometry. Chem Res Toxicol. 2021;34(10):2216-2226. https://doi.org/10.1021/acs.chemrestox.1c00253
37. Adermark L, Galanti MR, Ryk C, Gilljam H, Hedman L. Prospective association between use of electronic cigarettes and use of conventional cigarettes: a systematic review and meta-analysis. ERJ Open Res. 2021;7(3):00976-2020. https://doi.org/10.1183/23120541.00976-2020
38. World Health Organization. [homepage on the Internet]. Geneva: WHO;;c2022 [updated 2019 Dec 18; cited 2022 Jun 20]. WHO global report on trends in prevalence of tobacco use 2000-2025, third edition. Available from: https://www.who.int/publications-detail-redirect/who-global-report-on-trends-in-prevalence-of-tobacco-use-2000-2025-third-edition
39. Instituto Nacional de Câncer José Alencar Gomes da Silva. [homepage on the Internet]. Rio de Janeiro: INCA; c2022 [updated 2023 Feb 7; cited 2023 Jul 5]. Dados e números da prevalência do tabagismo - Página com informações estatísticas da prevalência do tabagismo no Brasil. Available from: https://www.inca.gov.br/observatorio-da-politica-nacional-de-controle-do-tabaco/dados-e-numeros-prevalencia-tabagismo
40. Instituto Nacional de Câncer José de Alencar Gomes da Silva; Pan American Health Organization, organizadores. Pesquisa especial de tabagismo - PETab: relatório Brasil. Rio de Janeiro (RJ) : Instituto Nacional do Câncer; Brasília (DF): Ministério da Saúde and Organização Pan-Americana da Saúde - Representação Brasil; 2011.
41. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde e Ambiente. Departamento de Análise Epidemiológica e Vigilância de Doenças Não Transmissíveis. [homepage on the Internet]. Brasília: o Ministério; c2023 [cited 2023 Nov 5]. Vigitel Brasil 2023: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2023. [Adobe Acrobat document, 133p.]. Available from https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/vigitel/vigitel-brasil-2023-vigilancia-de-fatores-de-risco-e-protecao-para-doencas-cronicas-por-inquerito-telefonico
42. Pinto M, Bardach A, Palacios A, Biz A, Alcaraz A, Rodriguez B, et al. Burden of smoking in Brazil and potential benefit of increasing taxes on cigarettes for the economy and for reducing morbidity and mortality. Cad Saude Publica. 2019;35(8):e00129118. https://doi.org/10.1590/0102-311X00129118
43. United States Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Smoking Cessation: A Report of the Surgeon General [monograph on the Internet]. Washington (DC): US Department of Health and Human Services; 2020. Available from: https://pubmed.ncbi.nlm.nih.gov/32255575/
44. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Estratégias para o cuidado da pessoa com doença crônica: o cuidado da pessoa tabagista (Cadernos de Atenção Básica, n. 40). Brasília: Ministério da Saúde, 2015. [Adobe Acrobat document, 156p.]. Available from: http://www.as.saude.ms.gov.br/wp-content/uploads/2016/06/caderno_40.pdf
45. Tanner NT, Kanodra NM, Gebregziabher M, Payne E, Halbert CH, Warren GW, et al. The Association between Smoking Abstinence and Mortality in the National Lung Screening Trial. Am J Respir Crit Care Med. 2016;193(5):534-541. https://doi.org/10.1164/rccm.201507-1420OC
46. Heiden BT, Eaton DB, Chang SH, Yan Y, Schoen MW, Chen LS, et al. The Impact of Persistent Smoking After Surgery on Long-term Outcomes After Stage I Non-small Cell Lung Cancer Resection. Chest. 2022;161(6):1687-1696. https://doi.org/10.1016/j.chest.2021.12.634
47. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA). Coordenação de Prevenção e Vigilância. Consenso sobre Abordagem e Tratamento do Fumante. Rio de Janeiro: INCA; 2001.
48. Reichert J, Araújo AJ, Gonçalves CM, Godoy I, Chatkin JM, Sales MP, et al. Smoking cessation guidelines--2008. J Bras Pneumol. 2008;34(10):845-880. https://doi.org/10.1590/s1806-37132008001000014
49. Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treatment tobacco use and dependence; 2008 guideline. [monograph on the Internet]. Rockville, MD: US Department of Health and Human Services [updated 2008 May 16; cited 2023 May 25]. Available from: https://stacks.cdc.gov/view/cdc/6964
50. Brasil. Ministério da Saúde. Instituto Nacional do Câncer [homepage on the Internet]. Brasília: Ministério da Saúde; c2023 [updated 2020 Sep 24; cited 2023 May 25]. Protocolo Clínico e Diretrizes Terapêuticas do Tabagismo. Available from: https://www.inca.gov.br/publicacoes/relatorios/protocolo-clinico-e-diretrizes-terapeuticas-do-tabagismo
51. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;2013(5):CD009329. https://doi.org/10.1002/14651858.CD009329.pub2
52. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016;2016(5):CD006103 https://doi.org/10.1002/14651858.CD006103.pub7
53. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2019;4(4):CD013308. https://doi.org/10.1002/14651858.CD013308
54. Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2020;4(4):CD000031. https://doi.org/10.1002/14651858.CD000031.pub5
55. Leone FT, Zhang Y, Evers-Casey S, Evins AE, Eakin MN, Fathi J, et al. Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202(2):e5-e31. https://doi.org/10.1164/rccm.202005-1982ST
56. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015;46(1):61-79. https://doi.org/10.1183/09031936.00092614
57. National Comprehensive Cancer Network Smoking cessation (version 1.2018). Available from: https://www.nccn.org/professionals/physician_gls/pdf/smoking.pdf
58. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018;72(25):3332-3365. https://doi.org/10.1016/j.jacc.2018.10.027
59. Hartmann-Boyce J, McRobbie H, Butler AR, Lindson N, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2021;9(9):CD010216. https://doi.org/10.1002/14651858.CD010216.pub6
60. Hanewinkel R, Niederberger K, Pedersen A, Unger JB, Galimov A. E-cigarettes and nicotine abstinence: a meta-analysis of randomised controlled trials. Eur Respir Rev. 2022;31(163):210215. https://doi.org/10.1183/16000617.0215-2021
61. Araujo LH, Baldotto C, Castro G Jr, Katz A, Ferreira CG, Mathias C, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44(1):55-64. https://doi.org/10.1590/S1806-37562017000000135
62. Ismael GFV, Coradazzi AL, Neto FAM, Abdalla KC, Milhomem P, Oliveira J. Aspectos clínicos e histopatológicos em câncer de pulmão: análise dos dados de uma instituição no interior paulista entre 1997 e 2008. Rev Bras Oncol Clinica. 2010;7(22):72-78.
63. Costa G, Thuler LC, Ferreira CG. Epidemiological changes in the histological subtypes of 35,018 non-small-cell lung cancer cases in Brazil. Lung Cancer Amst Neth. 2016;97:66-72. https://doi.org/10.1016/j.lungcan.2016.04.019
64. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA) [homepage on the Internet]. c2022 [updated 2022 Jul 18; cited 2022 Oct 5]. Câncer de pulmão. Available from: https://www.gov.br/inca/pt-br/assuntos/cancer/tipos/pulmao.
65. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2013. CA Cancer J Clin. 2013;63(1):11-30. https://doi.org/10.3322/caac.21166
66. Younes RN, Deutsch F, Badra C, Gross J, Haddad F, Deheinzelin D. Nonsmall cell lung cancer: evaluation of 737 consecutive patients in a single institution. Rev Hosp Clin Fac Med Sao Paulo 2004;59(3):119-127. https://doi.org/10.1590/s0041-87812004000300005
67. Costa GJ, Mello MJG, Bergmann A, Ferreira CG, Thuler LCS. Tumor-node-metastasis staging and treatment patterns of 73,167 patients with lung cancer in Brazil. J Bras Pneumol. 2020;46(1):e20180251.

https://doi.org/10.1590/1806-3713/e20180251

68. Westphal FL, Lima LC, Andrade EO, Lima Netto JC, Silva AS, Carvalho BC. Characteristics of patients with lung cancer in the city of Manaus, Brazil. J Bras Pneumol. 2009;35(2):157-163. https://doi.org/10.1590/s1806-37132009000200009
69. Barros JA, Valladares G, Faria AR, Fugita EM, Ruiz AP, Vianna GD, et al. Early diagnosis of lung cancer: the great challenge. Epidemiological variables, clinical variables, staging and treatment. J Bras Pneumol. 2006;32(3):221-227.
70. Novaes F, Cataneo D, Ruiz R, Defaveri J, Michelin O, Cataneo A. Lung cancer: Histology, staging, treatment and survival. J Bras Pneumol. 2008;34(8):595-600. https://doi.org/10.1590/s1806-37132008000800009
71. Araujo LH, Baldotto CS, Zukin M, Vieira FM, Victorino AP, Rocha VR, et al. Survival and prognostic factors in patients with Non-Small Cell Lung Cancer treated in private health care. Rev Bras Epidemiol. 2014;17(4):1001-1014. https://doi.org/10.1590/1809-4503201400040017
72. Mascarenhas E, Lessa G. Perfil clínico e sócio-demográfico de pacientes com câncer de pulmão não-pequenas células atendidos num serviço privado. Rev Bras Oncol Clínica. 2010;7(22):49-54.
73. Abrao FC, Abreu IRLB, Rocha RO, Munhoz FD, Rodrigues JHG, Younes RN. Impact of the delay to start treatment in patients with lung cancer treated in a densely populated area of Brazil. Clinics (Sao Paulo). 2017;72(11):675-680. https://doi.org/10.6061/clinics/2017(11)05
74. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for Lung Cancer with Low-Dose Computed Tomography: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;325(10):971-987. https://doi.org/10.1001/jama.2021.0377
75. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for Lung Cancer with Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 198. AHRQ Publication No. 20-05266-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2021 Mar.
76. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P; et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest. 2004;126(1):114-121. https://doi.org/10.1378/chest.126.1.114
77. Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, et al. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. Am J Respir Crit Care Med. 2008;178(9):956-961. https://doi.org/10.1164/rccm.200802-336OC
78. Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer. 2009;64(1):34-40. https://doi.org/10.1016/j.lungcan.2008.07.003
79. Saghir Z, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax. 2012;67(4):296-301. https://doi.org/10.1136/thoraxjnl-2011-200736
80. Becker N, Motsch E, Gross ML, Eigentopf A, Heussel CP, Dienemann H, et al. Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol. 2012;138(9):1475-1486. https://doi.org/10.1007/s00432-012-1228-9
81. Chiarantano RS, Vazquez FL, Franco A, Ferreira LC, Cristina da Costa M, Talarico T, et al. Implementation of an Integrated Lung Cancer Prevention and Screening Program Using a Mobile Computed Tomography (CT) Unit in Brazil. Cancer Control. 2022;29:10732748221121385. https://doi.org/10.1177/10732748221121385
82. Svartman FM, Leite MMR, Sartori APG, Gutierrez RS, Cadore AC, Oliveira CTM, et al. Lung cancer screening with low-dose CT integrated with pulmonary care in a public hospital in southern Brazil: results from the first 712 patients. J Bras Pneumol. 2022;48(5):e20220146. https://doi.org/10.36416/1806-3756/e20220146
83. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med. 2006;354(4):333-342. https://doi.org/10.1056/NEJMoa033250
84. Pinsky PF. Racial and ethnic differences in lung cancer incidence: how much is explained by differences in smoking patterns? (United States). Cancer Causes Control. 2006;17(8):1017-1024. https://doi.org/10.1007/s10552-006-0038-2
85. Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. Evaluation of USPSTF Lung Cancer Screening Guidelines Among African American Adult Smokers. JAMA Oncol. 2019;5(9):1318-1324. https://doi.org/10.1001/jamaoncol.2019.1402
86. US Preventive Services Task Force; Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, Caughey AB, et al. Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;325(10):962-970. https://doi.org/10.1001/jama.2021.1117
87. Wood DE, Kazerooni EA, Aberle D, Berman A, Brown LM, Eapen GA, et al. NCCN Guidelines® Insights: Lung Cancer Screening, Version 1.2022: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2022;20(7):754-764. https://doi.org/10.6004/jnccn.2022.0036
88. Penha D, Pinto E, Monaghan C, Hochhegger B, Marchiori E, Taborda-Barata L, et al. Incidental findings on lung cancer screening: pictorial essay and systematic checklist. J Bras Pneumol. 2022;48(1):e20210371. https://doi.org/10.36416/1806-3756/e20210371
89. Tanoue LT, Sather P, Cortopassi I, Dicks D, Curtis A, Michaud G, et al. Standardizing the Reporting of Incidental, Non-Lung Cancer (Category S) Findings Identified on Lung Cancer Screening Low-Dose CT Imaging. Chest. 2022;161(6):1697-1706. https://doi.org/10.1016/j.chest.2021.12.662
90. Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. 2018;153(4):954-985. https://doi.org/10.1016/j.chest.2018.01.016
91. Mazzone PJ, Silvestri GA, Souter LH, Caverly TJ, Kanne JP, Kathi HA, et al. Screening for Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. 2021;160(5):e427-e494. https://doi.org/10.1016/j.chest.2021.06.063
92. Kauczor HU, Baird AM, Blum TG, Bonomo L, Bostantzoglou C, Burghuber O, et al. ESR/ERS statement paper on lung cancer screening. Eur Respir J. 2020;55(2):1900506. https://doi.org/10.1183/13993003.00506-2019
93. Veronesi G, Baldwin DR, Henschke CI, Ghislandi S, Iavicoli S, Oudkerk M, et al. Recommendations for Implementing Lung Cancer Screening with Low-Dose Computed Tomography in Europe. Cancers (Basel). 2020;12(6):0. https://doi.org/10.3390/cancers12061672
94. Gierada DS, Black WC, Chiles C, Pinsky PF, Yankelevitz DF. Low-Dose CT Screening for Lung Cancer: Evidence from 2 Decades of Study. Radiol Imaging Cancer. 2020;2(2):e190058. https://doi.org/10.1148/rycan.2020190058
95. Shankar A, Saini D, Dubey A, Roy S, Bharati SJ, Singh N, et al. Feasibility of lung cancer screening in developing countries: challenges, opportunities and way forward. Transl Lung Cancer Res. 2019;8(Suppl 1):S106-S121. https://doi.org/10.21037/tlcr.2019.03.03
96. Kim H, Kim HY, Goo JM, Kim Y. Lung Cancer CT Screening and Lung-RADS in a Tuberculosis-endemic Country: The Korean Lung Cancer Screening Project (K-LUCAS). Radiology. 2020;296(1):181-188. https://doi.org/10.1148/radiol.2020192283
97. The World Bank [homepage on the Internet]. Washington (DC): The World Bank; c2023 [cited 2023 Jun 9]. Incidence of tuberculosis (per 100,000 people). Available from: https://data.worldbank.org/indicator/SH.TBS.INCD
98. Miranda-Filho A, Charvat H, Bray F, Migowski A, Cheung LC, Vaccarella S, et al. A modeling analysis to compare eligibility strategies for lung cancer screening in Brazil. EClinicalMedicine. 2021;42:101176. https://doi.org/10.1016/j.eclinm.2021.101176
99. Bach PB, Kattan MW, Thornquist MD, Kris MG, Tate RC, Barnett MJ, Hsieh LJ, Begg CB. Variations in lung cancer risk among smokers. J Natl Cancer Inst. 2003;95(6):470-478. https://doi.org/10.1093/jnci/95.6.470
100. Toumazis I, Bastani M, Han SS, Plevritis SK. Risk-Based lung cancer screening: A systematic review. Lung Cancer. 2020;147:154-186. https://doi.org/10.1016/j.lungcan.2020.07.007
101. Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. N Engl J Med. 2013;368(8):728-736. https://doi.org/10.1056/NEJMoa1211776
102. Tammemagi CM, Pinsky PF, Caporaso NE, Kvale PA, Hocking WG, Church TR, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst. 2011;103(13):1058-1068. https://doi.org/10.1093/jnci/djr173
103. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK.

Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. JAMA. 2016;315(21):2300-2311. https://doi.org/10.1001/jama.2016.6255

104. Cheung LC, Berg CD, Castle PE, Katki HA, Chaturvedi AK. Life-Gained-Based Versus Risk-Based Selection of Smokers for Lung Cancer Screening. Ann Intern Med. 2019;171(9):623-632. https://doi.org/10.7326/M19-1263
105. Ten Haaf K, Bastani M, Cao P, Jeon J, Toumazis I, Han SS, et al. A Comparative Modeling Analysis of Risk-Based Lung Cancer Screening Strategies. J Natl Cancer Inst. 2020;112(5):466-479. https://doi.org/10.1093/jnci/djz164
106. Katki HA, Kovalchik SA, Petito LC, Cheung LC, Jacobs E, Jemal A, et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Ann Intern Med. 2018;169(1):10-19. https://doi.org/10.7326/M17-2701
107. Moyer VA; US Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160(5):330-338. https://doi.org/10.7326/M13-2771
108. Kumar V, Cohen JT, van Klaveren D, Soeteman DI, Wong JB, Neumann PJ, et al. Risk-Targeted Lung Cancer Screening: A Cost-Effectiveness Analysis. Ann Intern Med. 2018;168(3):161-169. https://doi.org/10.7326/M17-1401
109. Teles GBDS, Macedo ACS, Chate RC, Valente VAT, Funari MBG, Szarf G. LDCT lung cancer screening in populations at different risk for lung cancer. BMJ Open Respir Res. 2020 Feb;7(1):e000455. https://doi.org/10.1136/bmjresp-2019-000455
110. Kazerooni EA, Austin JH, Black WC, Dyer DS, Hazelton TR, Leung AN, et al. ACR-STR practice parameter for the performance and reporting of lung cancer screening thoracic computed tomography (CT): 2014 (Resolution 4). J Thorac Imaging. 2014;29(5):310-316. https://doi.org/10.1097/RTI.0000000000000097
111. Fintelmann FJ, Bernheim A, Digumarthy SR, Lennes IT, Kalra MK, Gilman MD, et al. The 10 Pillars of Lung Cancer Screening: Rationale and Logistics of a Lung Cancer Screening Program. RadioGraphics. 2015;35(7):1893-1908. https://doi.org/10.1148/rg.2015150079
112. American Association of Physicists in Medicine. [homepage on the Internet]. Alexandria (VA): AAPM; c2023 [updated 2019 Sep 2019; cited 2023 Jun 13]. Lung Cancer Screening CT Protocols Version 5.1. Available from: https://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf
113. Vonder M, Dorrius MD, Vliegenthart R. Latest CT technologies in lung cancer screening: protocols and radiation dose reduction. Transl Lung Cancer Res. 2021;10(2):1154-1164. https://doi.org/10.21037/tlcr-20-808
114. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-243. https://doi.org/10.1148/radiol.2017161659
115. American College of Radiology Committee on Lung-RADS. [homepage on the Internet]. Reston (VA): ACR; c2023 [cited 2023 Jun 28]. Lung-RADS assessment categories version 1.1. Available from: www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf
116. American College of Radiology Committee on Lung-RADS. [homepage on the Internet]. Reston (VA): ACR; c2023 [updated 2022; cited 2023 Jun 20]. Lung CT Screening Reporting & Data System (Lung-RADS®). Available from: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads
117. Xu DM, Gietema H, de Koning H, Vernhout R, Nackaerts K, Prokop M, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer. 2006; 54(2):177-184. https://doi.org/10.1016/j.lungcan.2006.08.006
118. Devaraj A, van Ginneken B, Nair A, Baldwin D. Use of Volumetry for Lung Nodule Management: Theory and Practice. Radiology. 2017;284(3):630–644. https://doi.org/10.1148/radiol.2017151022
119. Revel MP, Bissery A, Bienvenu M, Aycard L, Lefort C, Frija G. Are two-dimensional CT measurements of small noncalcified pulmonary nodules reliable? Radiology. 2004;231(2):453-458. https://doi.org/10.1148/radiol.2312030167
120. Gierada DS, Rydzak CE, Zei M, Rhea L. Improved Interobserver Agreement on Lung-RADS Classification of Solid Nodules Using Semiautomated CT Volumetry. Radiology. 2020;297(3):675-684. https://doi.org/10.1148/radiol.2020200302
121. Heuvelmans MA, Walter JE, Vliegenthart R, van Ooijen PMA, De Bock GH, de Koning HJ, et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. Thorax. 2018;73(8):779-781. https://doi.org/10.1136/thoraxjnl-2017-210770
122. Zhao YR, van Ooijen PM, Dorrius MD, Heuvelmans M, de Bock GH, Vliegenthart R, Oudkerk M. Comparison of Three Software Systems for Semi-Automatic volumetry of Pulmonary Nodules on Baseline and Follow-Up CT Examinations. Acta Radiol 2014;55(6):691-698. https://doi.org/10.1177/0284185113508177
123. Delorme S, Kaaks R. Lung Cancer Screening by Low-Dose Computed Tomography: Part 2 - Key Elements for Programmatic Implementation of Lung Cancer Screening. Rofo. 2021;193(6):644-651. https://doi.org/10.1055/a-1290-7817
124. Pinsky PF, Gierada DS, Black W, Munden R, Nath H, Aberle D, et al. Performance of Lung-RADS in the National Lung Screening Trial. Ann Intern Med. 2015;162(7):485-491. https://doi.org/10.7326/M14-2086
125. Ho H, Williamson C, Regis SM, Stock CT, Quadri SM, McKee BJ, et al. Surgery and invasive diagnostic procedures for benign disease are rare in a large low dose computed tomography lung cancer screening program. J Thorac Cardiovasc Surg. 2021;161(3):790-802.e2. https://doi.org/10.1016/j.jtcvs.2020.08.109
126. Passiglia F, Cinquini M, Bertolaccini L, Del Re M, Facchinetti F, Ferrara R, et al. Benefits and Harms of Lung Cancer Screening by Chest Computed Tomography: A Systematic Review and Meta-Analysis. J Clin Oncol. 2021;39(23):2574-2585. https://doi.org/10.1200/JCO.20.02574
127. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess Winch Engl. 2016;20(40):1-146. https://doi.org/10.3310/hta20400
128. Dunn CE, Edwards A, Carter B, Field JK, Brain K, Lifford KJ. The role of screening expectations in modifying short-term psychological responses to low-dose computed tomography lung cancer screening among high-risk individuals. Patient Educ Couns. 2017;100(8):1572-1579. https://doi.org/10.1016/j.pec.2017.02.024
129. Penha D, Pinto E, Monaghan C, Hochhegger B, Marchiori E, Taborda-Barata L, et al. Incidental findings on lung cancer screening: pictorial essay and systematic checklist J Bras Pneumol. 2022;48(1):e20210371. https://doi.org/10.36416/1806-3756/e20210371
130. Clark MA, Gorelick JJ, Sicks JD, Park ER, Graham AL, Abrams DB, et al. The Relations Between False Positive and Negative Screens and Smoking Cessation and Relapse in the National Lung Screening Trial: Implications for Public Health. Nicotine Tob Res. 2016;18(1):17-24. https://doi.org/10.1093/ntr/ntv037
131. Iaccarino JM, Duran C, Slatore CG, Wiener RS, Kathuria H. Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review. Prev Med. 2019;121:24-32. https://doi.org/10.1016/j.ypmed.2019.02.016
132. Pedersen JH, Ashraf H. Implementation and organization of lung cancer screening. Ann Transl Med. 2016;4(8):152. https://doi.org/10.21037/atm.2016.03.59
133. van der Aalst CM, Ten Haaf K, de Koning HJ. Implementation of lung cancer screening: what are the main issues? Transl Lung Cancer Res. 2021;10(2):1050-1063. https://doi.org/10.21037/tlcr-20-985
134. Dobler CC, Midthun DE, Montori VM. Quality of Shared Decision Making in Lung Cancer Screening: The Right Process, With the Right Partners, at the Right Time and Place. Mayo Clin Proc. 2017;92(11):1612-1616. https://doi.org/10.1016/j.mayocp.2017.08.010
135. Field JK, deKoning H, Oudkerk M, Anwar S, Mulshine J, Pastorino U, et al. Implementation of lung cancer screening in Europe: challenges and potential solutions: summary of a multidisciplinary roundtable discussion. ESMO Open. 2019;4(5):e000577. https://doi.org/10.1136/esmoopen-2019-000577
136. Lin Y, Fu M, Ding R, Inoue K, Jeon CY, Hsu W, et al. Patient Adherence to Lung CT Screening Reporting & Data System-Recommended Screening Intervals in the United States: A Systematic Review and Meta-Analysis. J Thorac Oncol. 2021;17(1):38-55. https://doi.org/10.1016/j.jtho.2021.09.013
137. Pyenson B, Dieguez G. 2016 reflections on the favorable cost-benefit of lung cancer screening. Ann Transl Med. 2016;4(8):155. https://doi.org/10.21037/atm.2016.04.02
138. Pyenson BS, Tomicki SM. Lung Cancer Screening: A Cost-Effective Public Health Imperative. Am J Public Health. 2018;108(10):1292-1293. https://doi.org/10.2105/AJPH.2018.304659
139. Ten Haaf K, Tammemägi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. PLOS Med. 2017;14(2):e1002225. https://doi.

org/10.1371/journal.pmed.1002225

140. Grover H, King W, Bhattarai N, Moloney E, Sharp L, Fuller L. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. Lung Cancer. 2022;170:20-33. https://doi.org/10.1016/j.lungcan.2022.05.005
141. Liu CC, Shi JF, Liu GX, Tang W, Zhang X, Li F, et al. Cost-effectiveness of lung cancer screening worldwide: a systematic review [Article in Chinese]. Zhonghua Liu Xing Bing Xue Za Zhi Zhonghua Liuxingbingxue Zazhi. 2019;40(2):218-226. https://doi.org/10.3760/cma.j.issn.0254-6450.2019.02.018
142. Sun C, Zhang X, Guo S, Liu Y, Zhou L, Shi J, et al. Determining cost-effectiveness of lung cancer screening in urban Chinese populations using a state-transition Markov model. BMJ Open. 2021;11(7):e046742. https://doi.org/10.1136/bmjopen-2020-046742
143. Snowsill T, Yang H, Griffin E, Long L, Varley-Campbell J, Coelho H, et al. Low-dose computed tomography for lung cancer screening in high-risk populations: a systematic review and economic evaluation. Health Technol Assess. 2018;22(69):1-276. https://doi.org/10.3310/hta22690
144. International Early Lung Cancer Action Program Investigators; Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med. 2006;355(17):1763-1771. https://doi.org/10.1056/NEJMoa060476
145. Du Y, Sidorenkov G, Heuvelmans MA, Groen HJM, Vermeulen KM, Greuter MJW, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study. Eur J Cancer. 2020;135:121-129. https://doi.org/10.1016/j.ejca.2020.05.004
146. Hensing TA, Salgia R. Molecular biomarkers for future screening of lung cancer. J Surg Oncol. 2013;108(5):327-333. https://doi.org/10.1002/jso.23382
147. Seijo LM, Peled N, Ajona D, Boeri M, Field JK, Sozzi G, et al. Biomarkers in Lung Cancer Screening: Achievements, Promises, and Challenges. J Thorac Oncol. 2019;14(3):343-357. https://doi.org/10.1016/j.jtho.2018.11.023
148. Zaric B, Perin B, Carapic V, Stojsic V, Matijasevic J, Andrijevic I, et al. Diagnostic value of autofluorescence bronchoscopy in lung cancer. Thorac Cancer. 2013;4(1):1-8. https://doi.org/10.1111/j.1759-7714.2012.00130.x
149. Li Y, Zhang T, Zhang H, Wang X, Liu X, Huang Q, et al. Clinical Significance of P16 Gene Methylation in Lung Cancer. Adv Exp Med Biol. 2020;1255:133-142. https://doi.org/10.1007/978-981-15-4494-1_11
150. Hulbert A, Jusue-Torres I, Stark A, Chen C, Rodgers K, Lee B, et al. Early Detection of Lung Cancer Using DNA Promoter Hypermethylation in Plasma and Sputum. Clin Cancer Res. 2017;23(8):1998-2005. https://doi.org/10.1158/1078-0432.CCR-16-1371
151. Nardi-Agmon I, Abud-Hawa M, Liran O, Gai-Mor N, Ilouze M, Onn A, et al. Exhaled Breath Analysis for Monitoring Response to Treatment in Advanced Lung Cancer. J Thorac Oncol. 2016;11(6):827-837. https://doi.org/10.1016/j.jtho.2016.02.017
152. Peled N, Hakim M, Bunn P, Miller Y, Kennedy T, Mattei J, et al. Non-invasive Breath Analysis of Pulmonary Nodules. J Thorac Oncol. 2012;7(10):1528-1533. https://doi.org/10.1097/JTO.0b013e3182637d5f
153. Sozzi G, Boeri M, Rossi M, Verri C, Suatoni P, Bravi F, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol. 2014;32(8):768-773. https://doi.org/10.1200/JCO.2013.50.4357
154. Pastorino U, Boeri M, Sestini S, Sabia F, Milanese G, Silva M, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. Ann Oncol. 2022;33(4):395-405. https://doi.org/0.1016/j.annonc.2022.01.008
155. Sozzi G, Roz L, Conte D, Mariani L, Andriani F, Lo Vullo S, et al. Plasma DNA quantification in lung cancer computed tomography screening: five-year results of a prospective study. Am J Respir Crit Care Med. 2009;179(1):69-74. https://doi.org/10.1164/rccm.200807-1068OC
156. Rezola A, Pey J, Rubio Á, Planes FJ. In-Silico prediction of key metabolic differences between two non-small cell lung cancer subtypes. PLoS One. 2014;9(8):e103998. https://doi.org/10.1371/journal.pone.0103998
157. Cohn AL, Seiden M, Kurtzman KN, Hubbell E, Gross S, Venn O, et al. The Circulating Cell-free Genome Atlas (CCGA) Study: Follow-up (F/U) on non-cancer participants with cancer-like cell-free DNA signals. J Clin Oncol 2019;37□15_suppl):5574-5574. https://doi.org/10.1200/JCO.2019.37.15_suppl.5574
158. ClinicalTrials.gov [homepage on the Internet]. Bethesda: National Institutes of Health [updated 2022 Aug 20; cited 2023 Jun 9]. The Circulating Cell-free Genome Atlas Study (CCGA) [NCT02889978]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT02889978
159. McWilliams A, Tammemagi M, Mayo J, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening computed tomography. N Engl J Med. 2013;369(10):910-919. https://doi.org/10.1056/NEJMoa1214726

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Connective tissue disease-associated interstitial lung disease

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ABSTRACT

Connective tissue disease-associated interstitial lung disease (CTD-ILD) represents a group of systemic autoimmune disorders characterized by immune-mediated organ dysfunction. Systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myositis, and Sjögren's syndrome are the most common CTDs that present with pulmonary involvement, as well as with interstitial pneumonia with autoimmune features. The frequency of CTD-ILD varies according to the type of CTD, but the overall incidence is 15%, causing an important impact on morbidity and mortality. The decision of which CTD patient should be investigated for ILD is unclear for many CTDs. Besides that, the clinical spectrum can range from asymptomatic findings on imaging to respiratory failure and death. A significant proportion of patients will present with a more severe and progressive disease, and, for those, immunosuppression with corticosteroids and cytotoxic medications are the mainstay of pharmacological treatment. In this review, we summarized the approach to diagnosis and treatment of CTD-ILD, highlighting recent advances in therapeutics for the various forms of CTD.

Keywords: Lung diseases, interstitial; Collagen diseases; Scleroderma, systemic; Arthritis, rheumatoid; Myositis; Therapeutics.

INTRODUCTION

A group of systemic autoimmune illnesses known as connective tissue diseases (CTDs) are defined by immune-mediated organ failure. All CTDs have a chance of developing to interstitial lung disease (ILD), but some individuals have a higher risk of developing it, such as those who have systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), Sjögren's syndrome (SS), mixed CTD, and systemic lupus erythematosus (SLE).[1] In some cases, a definitive CTD diagnosis is not possible despite some suggestive clinical and laboratorial findings. This is called interstitial pneumonia with autoimmune features (IPAF). The main hypothesis for the pathogenesis of CTD-ILD is that fibrosis is preceded by an immune-mediated process that has distinct features in SSc, RA, IIM, and SS.[2]

Patients with CTD-ILD with decreased FVC and/or DL_{CO}, and fibrotic signs on HRCT have a worse prognosis than do those with CTD without ILD. Knowledge on ILD influences treatment choices and directs surveillance. However, who should be screened for ILD is not well established for CTDs, with the exception of SSc, in whom HRCT should be done at the moment of diagnosis. Additionally, HRCT can assist to determine the extent and severity of the disease since the presence of bronchiectasis and honeycombing is linked to a higher risk of progression.[3] Another difficult decision is how patients should be monitored, in which cases ILD should be treated, and in whom the therapy should be discontinued.

The management of CTD-ILD is the main topic of this review. Therefore, treatment of comorbid conditions such as pulmonary hypertension, gastroesophageal reflux, airway disease, and bone health will not be addressed.

SSC-ASSOCIATED ILD

SSc is characterized by autoimmunity, vasculopathy, and fibrosis, and may be associated with a high mortality rate.[4] ILD is a common disease feature and, along with pulmonary hypertension, represents the main cause of death. As a result, ILD evaluation is advised as a part of the initial assessment and follow-up of patients with SSc.[5] Every patient should receive an ILD-related physical examination with special attention to the presence of crackles since this is a marker of fibrosis and, consequently, of disease severity. Screening should be done with HRCT, FVC measurement, and, when available, DL_{CO} determination, for all SSc patients at baseline. Nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) are the most common ILD patterns linked to SSc, and their estimated prevalence ranges from 30-40% in clinically relevant cases to up to 80% in asymptomatic presentations. For longitudinal follow-up, in the first 3-5 years after disease diagnosis, pulmonary function tests (PFTs) should be performed every 3-6 months. HRCT should be performed every 12-24 months, depending on the risk of disease progression. High risk factors, such as lower FVC and DL_{CO}, increases in disease extension on

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HRCT, or presence of anti-Scl-70, should prompt more frequent HRCT (every 12 months). New onset of symptoms or changes in PFT results requires close evaluation (Figure 1).[6-8]

The likelihood of disease progression, the degree of extrapulmonary disease, and the patient's risk of developing severe disease should all be taken into account when deciding whether to start treatment.[7] Also, it is important to evaluate risk factors for disease progression, such as African-American ethnicity, older age at disease onset, male sex, short disease duration, and presence of anti-Scl-70 or RNA polymerase III. Therefore, patients with subclinical disease—asymptomatic patient, minimal-to-mild extension of ILD on HRCT, normal pulmonary function—and with low risk factors for ILD could be monitored in a certain way. However, patients with clinical ILD or subclinical ILD who are highly at risk of disease progression should be started on pharmacological therapy.

Treatment of SSc is challenging because of its heterogeneous disease manifestations, and the preference is for therapies that may target more than one active organ system. However, SSc is the CTD-ILD with the most robust scientific evidence. Treatment includes the use of immunosuppressants and antifibrotics (Figure 2).

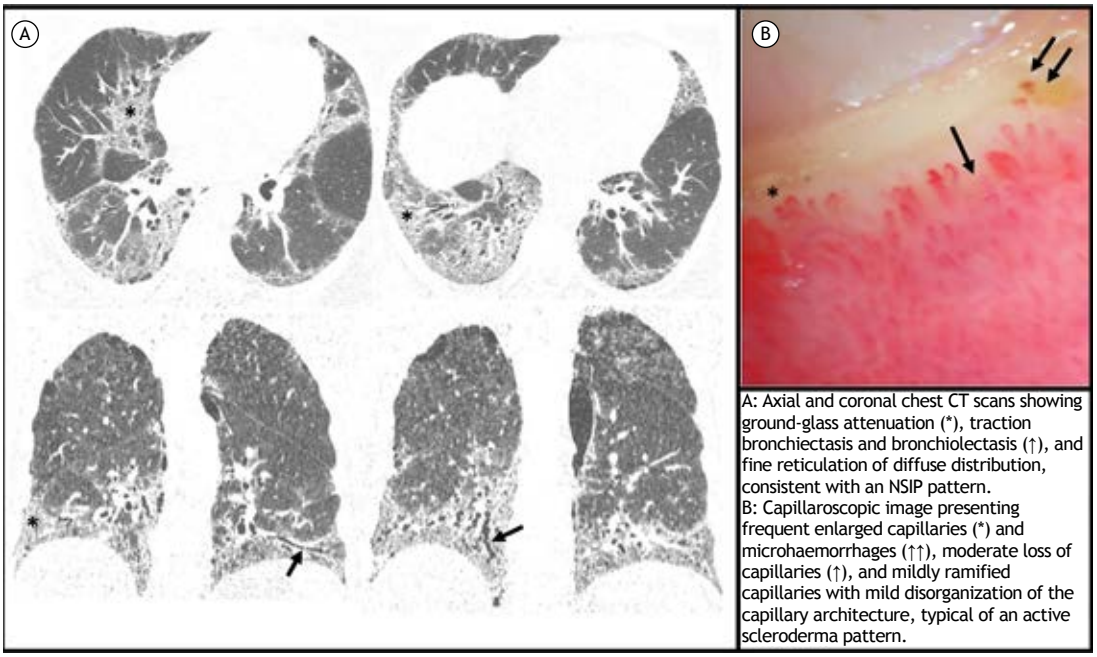
Due to the increased risk of scleroderma-related renal crises, corticosteroids should be prescribed with caution in SSc patients.[9]

Cyclophosphamide modulates regulatory T cells, decreasing the secretion of IFN-γ and IL-12. Tashkin et al.,[10] based on the Scleroderma Lung Study (SLS) I, found that cyclophosphamide was linked to improvements n FVC in % of predicted values (FVC%) after 12 months of oral cyclophosphamide (2 mg/kg per day) over placebo and that the benefit was sustained for 24 months. However, adverse events were more common in the cyclophosphamide group.

Mycophenolate impairs both T-cell proliferation and B-cell proliferation. In the SLS II, the use of mycophenolate for 24 months (1,500 mg twice daily) was compared with 12 months of oral cyclophosphamide (2 mg/kg per day).[11] With regard to efficacy endpoints, there was no discernible difference between treatments; however, mycophenolate showed less toxicity. Hence, mycophenolate emerged as a first-line therapy for SSc-ILD.[12] If mycophenolate cannot be tolerated, intravenous pulses of cyclophosphamide could be used at 750 mg/m^2 monthly.

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor. Both phase 2 and phase 3 trials of tocilizumab versus placebo for early diffuse cutaneous SSc showed no significant difference in the primary outcome, skin fibrosis.[13,14] The secondary endpoint (changes from baseline FVC%) in the phase 3 trial revealed a significant difference at 48 weeks, favoring tocilizumab.[14] A post-hoc analysis revealed that patients with fibrosis (65%) had FVC% stabilization.[15] Even though there have been no tests comparing tocilizumab with mycophenolate or cyclophosphamide, this finding suggests that tocilizumab may be an option for individuals with early disease-related cutaneous SSc-associated ILD and high C-reactive protein levels.

Rituximab is an anti-CD20 monoclonal antibody that depletes peripheral B cells. A randomized controlled trial (RCT) of rituximab (375 mg/m^2 once weekly) versus placebo for four weeks led to significant improvement in skin fibrosis,[16] but 89% of the patients had ILD, and



A: Axial and coronal chest CT scans showing ground-glass attenuation (*), traction bronchiectasis and bronchiolectasis (↑), and fine reticulation of diffuse distribution, consistent with an NSIP pattern.
B: Capillaroscopic image presenting frequent enlarged capillaries (*) and microhaemorrhages (↑↑), moderate loss of capillaries (↑), and mildly ramified capillaries with mild disorganization of the capillary architecture, typical of an active scleroderma pattern.

Figure 1. HRCT scans (in A) and capillaroscopy features (in B) in a patient with systemic sclerosis. NSIP: nonspecific interstitial pneumonia.

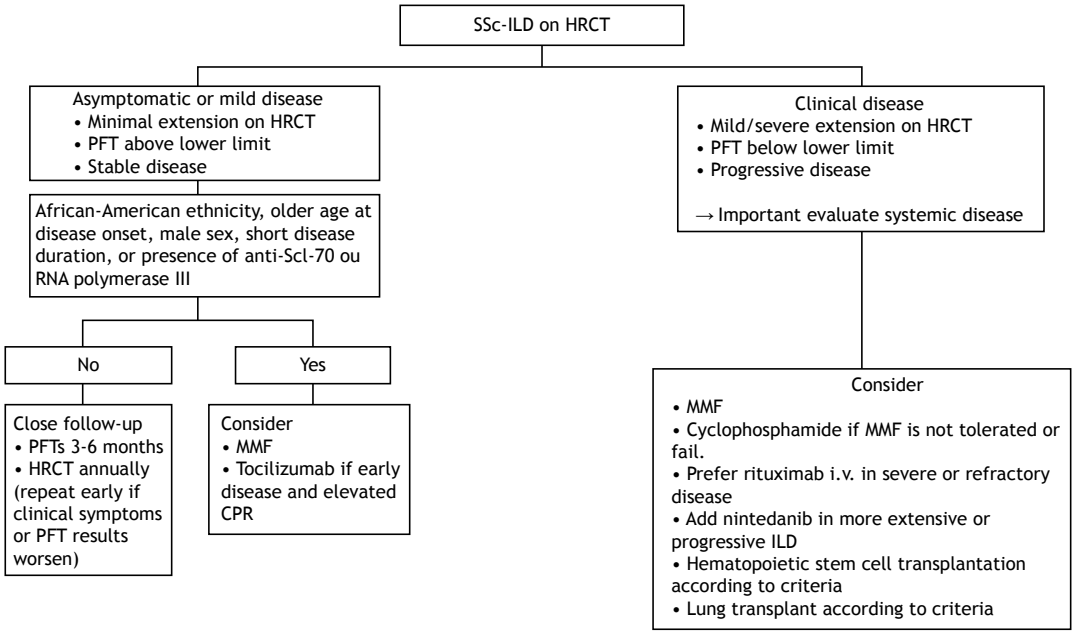


Figure 2. Treatment algorithm for systemic sclerosis-associated interstitial lung disease (SSc-ILD) based on evidence and expert opinion. PFT: pulmonary function test; MMF: mycophenolate; and CPR: C-reactive protein. Modified from Roofeh et al.[7]

there was a favorable effect on changes in FVC% at six months.[17] A phase 2 RCT of rituximab (designated RECITAL) used 1,000 g at day 0 and at day 15 versus a monthly pulse of intravenous cyclophosphamide 600 mg/m^2 in severe or progressive CTD-ILD patients and showed that FVC% improved from baseline in both arms after four months, but rituximab caused fewer adverse events.[18] The study included 38% of patients with SSc.[18] Individuals with refractory multisystemic disease are difficult to treat and rely heavily on expert judgment. If mycophenolate fails, one option is to replace it with cyclophosphamide[19] or rituximab.[20]

Nintedanib is an antifibrotic medication that blocks tyrosine-kinase receptors (PDGF and VEGF receptors). An RCT (SENSCIS) in patients with SSc-ILD compared nintedanib 150 mg twice a day with placebo in patients showing fibrosis affecting at least 10% of the lungs and showed that the nintedanib arm had a slower rate of decline in FVC over 52 weeks.[21] Prior to enrollment, 48% of patients were taking a stable dose of mycophenolate, and patients assigned to receive mycophenolate plus nintedanib had the slowest decline in lung function. However, it is important to notice that patients in that RCT were randomized for nintedanib but not for mycophenolate. Patients who had early SSc, elevated inflammatory markers, or extensive skin fibrosis had a more rapid decline in FVC, and nintedanib had a numerically greater effect on these patients.[22] Nintedanib was also studied in patients with progressive pulmonary fibrosis in the RCT designated INBUILD.[23] Almost a quarter of the patients had CTD-ILD (mostly SSc and RA). Although the study lacked power to show subgroup efficacy, it did show an overall reduction in ILD progression. Nintedanib is not typically used as first-line therapy, because no improvement in lung function has been shown in any study.

Pirfenidone is also an antifibrotic whose precise pharmacodynamics is yet to be known. It has been confirmed that it inhibits TGF-β expression and PDGF production, as well as having an anti-inflammatory effect. A phase 2 trial in patients with SSc-ILD (LOTUSS) evaluated pirfenidone with either 2- or 4-week titration up to 2,403 mg/day for 16 weeks.[24] SLS III is an RCT that compared the combination of mycophenolate plus pirfenidone, mycophenolate alone, and placebo.[25] Recruitment was prematurely stopped due to COVID-19, and only one-third of the calculated sample size was included. There was no difference in adding pirfenidone to the mycophenolate regimen in an 18-month period, and both groups showed improvements in FVC% when compared with placebo, although the combination mycophenolate plus pirfenidone presented with a more rapid improvement over 6 months and showed a trend toward fewer fibrosis areas on HRCT.

According to a recent American Thoracic Society (ATS) guideline,[26] the evidence for treatment of SSc-ILD is strong for mycophenolate and conditional for cyclophosphamide, tocilizumab, rituximab, nintedanib, and mycophenolate plus nintedanib. The recommendation for the use of pirfenidone requires further research, and the use of corticosteroids should be done with caution, with doses of no more than 15 mg/day.

Hematopoietic autologous stem cell transplantation has emerged as a therapy capable of the greatest improvements in ILD and skin disease. However, because of its high potential for life-threatening adverse effects, it is usually a second-line therapy in patients with early diffuse SSc and a first-line approach after failure. Three trials have presented improvements in survival, skin fibrosis, FVC, and quality of life when compared with therapy with cyclophosphamide.[6]

RA-ASSOCIATED ILD

RA is a chronic, inflammatory disease that affects more women than men and peaks in the sixth decade of life. ILD is one of the most common and severe complications of RA, accounting for 10-20% of deaths (the second leading cause).

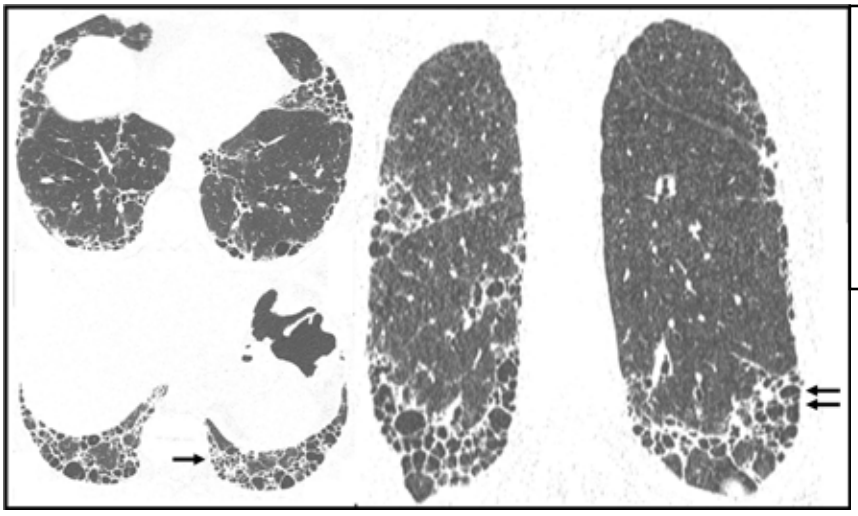
The estimated prevalence of clinically significant RA-ILD is between 10% and 30% and, differently from other CTD-ILD, UIP is the most common pattern (Figure 3).[8,27] Because non-UIP patients respond better to anti-inflammatory and immunosuppressive therapy, identifying the pattern could have therapeutic implications. Recommendations for initial evaluation and follow-up of patients with RA are less clear than are those for SSc, but the possibility of ILD should be considered based on its incidence and prevalence. For initial screening, patients who exhibit symptoms or Velcro crackles on respiratory auscultation should undergo HRCT and PFT (FVC and DL_{CO}). When there are no symptoms and auscultation is unremarkable, the choice for screening should be individualized on the basis of risk variables such male sex, advanced age, late onset of disease, disease duration, history of smoking, elevated rheumatoid factor and/or anticitrullinated protein levels, and disease activity.[27,28] There is some evidence that chest X-ray, spirometry, and pulse oximetry findings could identify pulmonary involvement in respiratory asymptomatic patients with RA.[29]

Disease activity should be monitored with clinical evaluation, PFTs, and six-minute walk tests every 3-6 months and with HRCT every 12-24 months, or if functional deterioration, treatment adjustments, or other respiratory complications are suspected.[6,28] The course of RA-ILD is varied. After diagnosis, some individuals have steady or even improved lung function results, while others experience lung function deterioration that is typically moderate but can occasionally be sudden.[30]

Usually, half of RA-ILD patients will have stable or slowly progressing ILD; therefore, risk factors for progression, such as UIP pattern, increased anticitrullinated protein levels, degree of worsening from baseline of PFT results, and significant fibrotic alterations on HRCT, should be monitored. A few studies, however, have shown that, after controlling for age, smoking, and PFT, UIP pattern is not an independent predictor of mortality.[31]

The treatment of RA-ILD is complex for various reasons. First, there have been few controlled studies on RA-ILD. Second, both conventional and biological disease-modifying antirheumatic drugs (DMARDs) have been linked to pulmonary toxicity. Third, there is no evidence that RA treatment reduces lung involvement, and immunosuppressive drugs commonly used to treat ILD do not always control the articular disease. This means that treating ILD secondary to RA is not the same as treating RA in a patient who also has ILD. Close monitoring is usually required in an asymptomatic patient with nonprogressive ILD (Figure 4).

Methotrexate is an important conventional DMARD (cDMARD) for RA treatment. Pulmonary toxicity of methotrexate is rare and, when present, it is subacute, presents as a hypersensitivity pneumonitis, usually occurring during the first year of treatment, and is dose dependent. However, an increasing body of evidence has revealed that methotrexate is negatively related to the occurrence of RA-ILD and does not appear to raise the risk of ILD.[32] As a result, in individuals with



Axial chest CT showing reticulation, traction bronchiectasis and bronchiolectasis (↑), and honeycombing (↑↑) with basal predominance, consistent with a UIP pattern. Coronal slice showing a straight interface between fibrosis and normal lung - straight-edge sign.

Figure 3. HRCT features in a patient with rheumatoid arthritis. UIP: usual interstitial pneumonia.

ILD, a personalized assessment for methotrexate use is advised.

Corticosteroids alone or in combination with cDMARDs or immunosuppressive drugs are usually used in the treatment of RA-ILD. Nevertheless, a British study discovered that patients with RA-ILD had a greater mortality rate when using long-term corticosteroid therapy due to an increased incidence of infection.[33] It is important to notice that there is lack of evidence from controlled studies, and recommendations are extrapolated from idiopathic pulmonary fibrosis and other CTD-ILD cohorts.

Mycophenolate and cyclophosphamide are also options for first-line treatment of RA-ILD, although there are no large RCTs. Mycophenolate (2,000-3,000 mg/day) was associated with improvement in symptoms and PFT results in CTD-ILD cohorts that included RA-ILD patients.[34] In patients with non-UIP pattern, there was improvement in FVC% and DL_{CO}% and, in cases with a UIP pattern, there was stabilization.[35] Cyclophosphamide is used in clinical practice, especially in cases of rapid progression of ILD, but with limited efficacy data.[36] Mycophenolate is considered the main alternative to cyclophosphamide due to the lower rate of side effects and possible better survival.[37] Because cyclophosphamide and mycophenolate do not normally control articular disease, they are often used with other immunosuppressants.[38]

Treatment options with other DMARDs, such as biologic (bDMARD) or targeted synthetic (tsDMARD) DMARDs require distinguishing between treating RA in a patient who also has ILD and treating a patient with ILD associated with RA. Furthermore, most studies lacked a control group and excluded patients with active ILD. As a result, conclusions about those treatments are largely subjective and based in opinion.

All anti-TNF-α agents have been associated with lung toxicity, with a prevalence of 0.5-3.0%.[39] It usually occurs within the first six months after treatment initiation, is usually severe, and has high mortality rates. Age, pre-existing ILD, and concurrent use of methotrexate or leflunomide are all risk factors for the development of this complication.[38] Experimental investigations suggest that anti-TNF-α could have both profibrotic and antifibrotic actions. Therefore, an imbalance between these two roles may trigger or stabilize ILD.[40] In patients with RA who are using anti-TNF-α and present with stable ILD, there is no conclusive evidence about discontinuation of the drug.

Treatment with tocilizumab (8 mg/kg i.v. every 4 weeks or 162 mg s.c. weekly) in RA-ILD patients has conflicting published data, because it could be associated with the development of ILD, with worsening of pre-existing ILD,[41] and with improvement or stabilization of lung function.[42] Furthermore, there is evidence that the worsening of ILD could be related to RA disease activity more than to drug toxicity.[43]

Abatacept is emerging as a safer alternative for RA-ILD patients who require biological therapy.[44] However, in a retrospective cohort analysis, there was no difference in the risk of ILD-related complications with the use of abatacept, rituximab, or tocilizumab when compared with anti-TNF-α therapy.[45]

Rituximab is also the preferred DMARD to treat RA articular activity when RA-ILD is present because of its articular and pulmonary efficacy,[46] with low incidence of new cases of ILD (0.4%), which is probably associated to disease activity rather than to drug toxicity.[47] Moreover, there is evidence of stabilization of ILD in progressive RA-ILD.[48,49] Some evidence suggests that long-term rituximab treatment raises the risk of respiratory or urinary infections as a result of the development of the side effect of hypogammaglobulinemia.[50]

Patients treated with tofacitinib (a Janus kinase inhibitor), when compared with those treated with adalimumab, had a decreased incidence of ILD, according to a retrospective study with a large cohort of RA patients, a finding that indicates that tofacitinib might have a good safety profile.[30,39]

Antifibrotics such as nintedanib have been shown in an RCT to slow the progression of fibrotic RA-ILD with a progressive phenotype.[23] In that RCT, progressive pulmonary fibrosis (PPF) was defined as meeting at least one of the following four criteria within the last 24 months: a relative decline of at least 10% of FVC%; a relative decline of at least 5% of FVC% plus

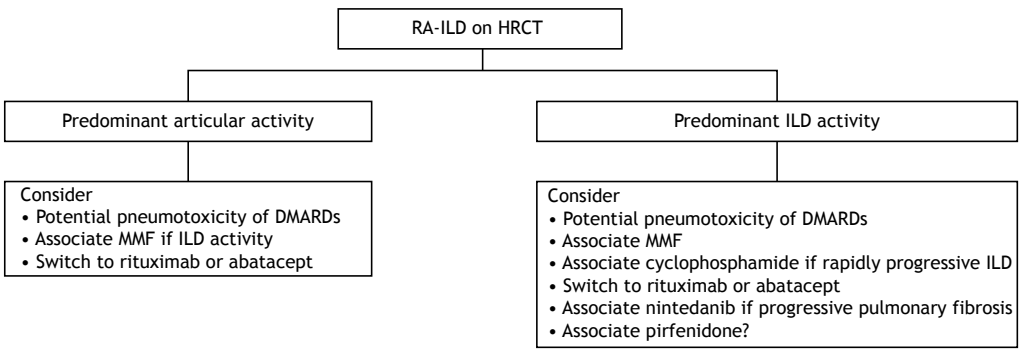


Figure 4. Treatment algorithm for rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on evidence and expert opinion. DMARDs: disease-modifying anti-rheumatic drugs; and MMF: mycophenolate.

worsening of respiratory symptoms; increase in fibrosis on HRCT; or worsening of respiratory symptoms and increase in fibrosis on HRCT. Regarding pirfenidone, a phase 2 RCT comparing the effectiveness of oral pirfenidone (2,403 mg/day) with that of placebo in patients with RA-ILD was terminated early due to slow recruitment secondary to COVID-19.[51] Although the primary endpoint was not met, results suggest that the pirfenidone group had a slower rate of decline of FVC. A single-center prospective controlled cohort study involving CTD-ILD patients (RA-ILD patients, 17%) compared the use of pirfenidone with a control group and found improvement in DL_{CO} in the pirfenidone RA-ILD group.[52] Recently, an official ATS/European Respiratory Society (ERS)/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* clinical practice guideline[53] has defined the concept of PPF with some differences when compared with a previous RCT on the topic.[23] The committee has suggested the use of nintedanib for the treatment of PPF, but not of pirfenidone, suggesting further research regarding that drug.

Important nonpharmacological interventions include smoking cessation, respiratory rehabilitation, immunization, and long-term oxygen therapy when indicated.

IIM

Immune-mediated muscle injury characterizes a group of illnesses known as idiopathic inflammatory myositis. There are many illnesses that afflict adults, such as dermatomyositis, polymyositis, and antisynthetase syndrome (AS). The pathogenesis and clinical presentation of each condition varies, particularly in terms of the presence or absence of extramuscular symptoms, such as skin and lung involvement.

New classification criteria were validated in 2017 by the European League Against Rheumatism and the American College of Rheumatology (ACR).[54] These criteria classified patients as having "definite", "probable", or "possible" disease. The presence of autoantibodies could be identified in over 50% of patients, and they can be divided in myositis-associated autoantibodies—anti-Ro52, anti-RNP, anti-Ku, anti-Pm Scl—and myositis-specific autoantibodies—anti-tRNA, anti-MDA5, anti-Mi2, anti-SRP, anti-TIF1g, and anti-NXP2. Also, antibodies bound to the cytoplasm are frequently seen with screening for antinuclear antibodies. AS is characterized by mechanic's hands, Raynaud's phenomenon, and the presence of anti-aminoacyl tRNA synthetase (ARS) antibodies. These cases are usually amyopathic.

With prevalence between 17% and 36%, ILD is the most common extrapulmonary involvement in IIM and the main cause of death. Patients with AS have an increased risk of ILD, and it may precede muscle symptoms in up to 20% of cases.[55] The exact distribution of radiological patterns of ILD stratified by different myositis-specific autoantibodies remains unclear, but HRCT can present with an organizing pneumonia pattern, an NSIP pattern, or an overlap of these two, especially in patients with ARS and anti-MDA5 antibodies (Figure 5). The UIP pattern is less common and may have a better prognosis than in idiopathic pulmonary fibrosis patients. CTD-associated UIP is more closely associated with signs such as the straight-edge sign, exuberant honeycombing, and anterior upper lobe sign.[56] Fibrotic ILD is associated with a worse prognostic.

There are no established guidelines for the treatment of IIM-ILD; instead, treatments vary widely and are frequently based on case studies or retrospective evaluations. An important differentiation should be made between chronic ILD, in which low-dose corticosteroids associated or not with immunosuppressive therapy will be needed, and rapidly progressive ILD, which often requires a more aggressive combination of immunosuppressive drugs (Figure 6).

Corticosteroids are the mainstay of IIM-ILD therapy and are typically used as a first-line strategy. Stable patients should receive 0.5-1.0 mg/kg per day of prednisone or its equivalent for 4 to 8 weeks, followed by gradual tapering over months.[57] Muscle enzyme levels may serve as guidance for tapering (when initially increased). A meta-analysis showed improvement rates with the use of corticosteroids alone in 89% of cases.[57] For rapidly progressive and severe disease, pulses of 1,000 mg of methylprednisolone could be used for 3 days. Data suggest that, in such cases, corticosteroids alone should have response rates of 50% and immunosuppressive therapy should be combined in advance.[55,57] Additional immunosuppressive drugs (steroid-sparing agents) could be used in patients who do not respond to or tolerate corticosteroid tapering.

Calcineurin inhibitors (cyclosporine A and tacrolimus) act by inhibiting IL-2-mediated CD4 T cell activation. Cyclosporine can be used in a dose of 4 mg/kg per day, maintaining plasma levels between 300 and 350 ng/mL, with improvement rates of 75%.[57] Tacrolimus is also an option.[58]

Azathioprine is a purine analogue that also blocks T-cell and B-cell proliferation. There are relatively few retrospective studies reporting safety in about two-thirds of ILD cases, with typical dosages of 2-3 mg/kg per day, showing good safety profile.[55] However, it is difficult to evaluate response, because many studies had different IIM diagnoses (which overlapped IIM/SSc and AS) and rarely described criteria response.[59]

Mycophenolate at a dose of 2,000-3,000 mg/kg per day is commonly used to treat IIM-ILD, and several studies have shown that it can stabilize or improve PFT results while reducing daily steroid doses.[33,60] One study suggests an efficacy of approximately 80% in treating IIM-ILD with a good safety profile.[55]

The use of cyclophosphamide is usually limited to most aggressive forms of IIM-ILD, favoring i.v. administration, and has been shown to improve both muscle strength and FVC and DL_{CO}.[61] It has also

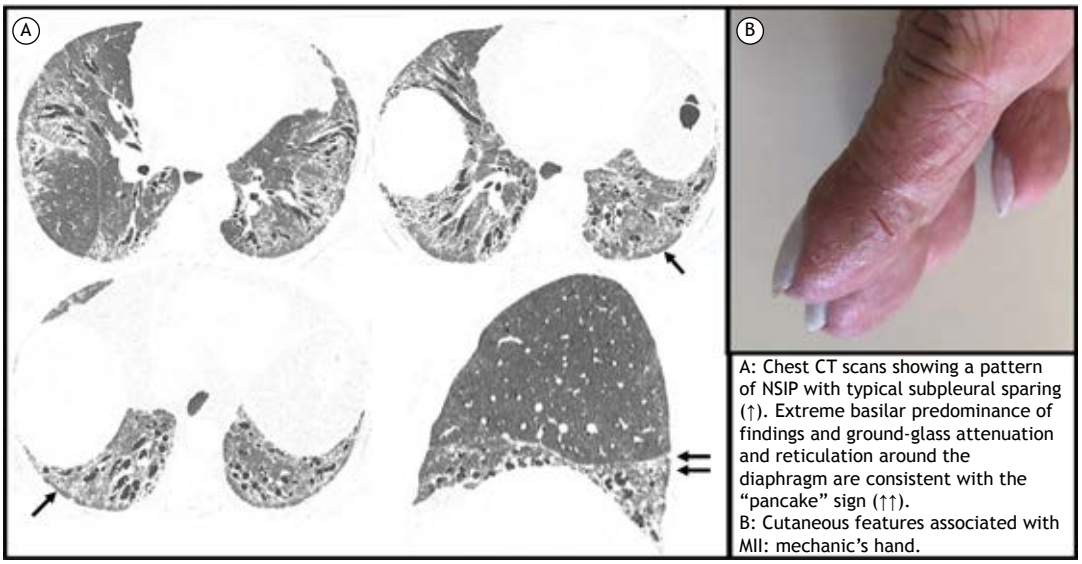


Figure 5. HRCT scans (in A) and cutaneous features (in B) in idiopathic inflammatory myopathy (IIM). NSIP: nonspecific interstitial pneumonia.

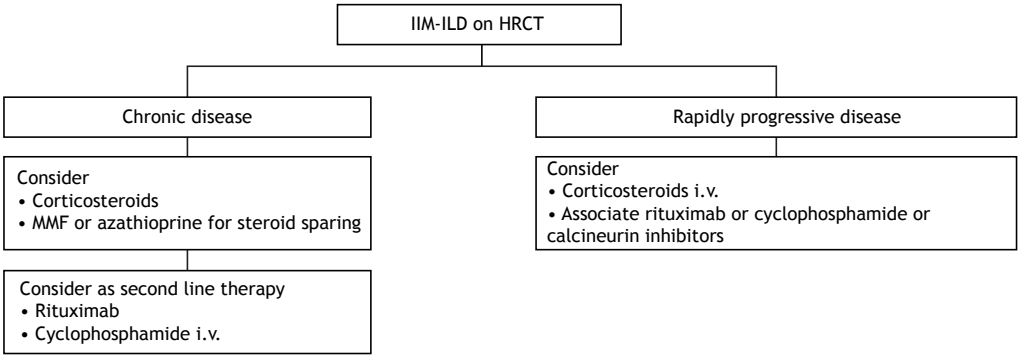


Figure 6. Treatment algorithm for idiopathic inflammatory myositis-associated interstitial lung disease (IIM-ILD) based on evidence and expert opinion. MMF: mycophenolate. Modified from Barba et al.[57] and Morisset et al.[59]

been used with cyclosporine A and a corticosteroid in cases of rapidly progressive disease or when initial management fails. A phase 2 RCT comparing the use of cyclophosphamide and that of rituximab in CTD-ILD patients, 45% of whom had IIM, showed that both arms had increases in FVC with no superiority of rituximab.[18] However, the rituximab arm experienced fewer adverse events.

Rituximab 1,000 mg at day 0 and day 15 has been shown to improve IIM-ILD in several retrospective studies.[62-64] Patients with IIM-ILD (particularly AS) appear to respond better than do patients with other CTD-ILD.[65] Rituximab is also the drug of choice in cases of refractory IIM-ILD. Intravenous immunoglobulin (more commonly used for active muscle disease) and tofacitinib (a Janus kinase inhibitor) are also described as potential treatments.[66]

OTHER CTDS

Here we remark some treatment information for CTD-ILD with more scarce data. Besides that, patients with SLE appear to have ILD less frequently and less severe disease when compared with patients with other CTDs. Therefore, we will not address SLE.

SS

The second most prevalent multisystemic disease after RA is SS. It is more common in women and is characterized by lymphocytic inflammation of exocrine glands, which causes dry eyes and mouth. A large proportion of asymptomatic patients will have abnormal pulmonary imaging, and 10% to 20% of patients will show significant pulmonary involvement.[67]

Prevalence seems to increase over time. Therefore, the ACR published a consensus guideline for SS in 2021.[68] A baseline chest X-ray is recommended for asymptomatic patients, and baseline PFTs are being considered. For symptomatic patients, they recommend HRCT and a complete PFT.[68] Bronchiolitis and bronchiectasis are the most common pulmonary manifestations, but, when present, ILD will manifest as NSIP, UIP, and/or lymphocytic interstitial pneumonia.

SS patients have an increased risk of lymphoma and amyloidosis.[69] Except for ILD with a UIP pattern,[68] a large proportion of the ILDs in SS-ILD patients tend to follow an indolent course.[68]

Corticosteroids are usually prescribed (0.5-1.0 mg/kg per day) and are frequently combined with immunosuppressive drugs such as mycophenolate and azathioprine.[70,71] The ACR guideline recommends second-line therapy with rituximab, cyclosporine, or tacrolimus in cases of moderate to severe ILD in patients who have failed or not tolerated mycophenolate.[68] Nintedanib, either alone or in combination with immunomodulatory agents, should be considered as second-line therapy when fibrotic ILD develops into PPF.[23] Patients with rapidly progressive disease should use intravenous corticosteroids with or without the addition of cyclophosphamide or rituximab.[18,55]

IPAF

Many ILD patients have clinical and/or laboratory characteristics that suggest background autoimmunity, but they lack a CTD that can be distinguished. To classify these patients, the ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD advocated using the name "IPAF," which is a combination of three domains.[72] A clinical domain consisting of extrathoracic characteristics; a serological domain of specific antibodies; and a morphological domain consisting of specific HRCT patterns, histological features, and multicompartment features. Those criteria were reviewed recently, offering insights for future directions with these patients.[73]

The most prevalent findings in IPAF populations evaluated by several centers around the world included female sex, Raynaud's phenomenon, positivity for antinuclear antibodies, and NSIP.[74] Predictors of mortality were age and DL_{CO}. When the HRCT pattern was analyzed, the presence of honeycombing predicted worse survival.[75] Additionally, a meta-analysis revealed that autoantibodies that are highly specific for particular CTDs (serological domains) are less significant in the prognosis of IPAF when compared with radiological-pathological patterns.[76]

There are still many questions regarding IPAF treatment. According to most studies, individuals with non-UIP IPAF have a survival rate comparable to that of individuals with CTD-ILD, and most ILD experts would likely treat them similarly. However, a proportion of IPAF patients demonstrated long-term stability with no treatment. Therefore, IPAF patients may be followed up without medication therapy or be treated with immunomodulation with glucocorticoids and/or immunosuppressants including mycophenolate, azathioprine, cyclophosphamide, calcineurin inhibitors (cyclosporine and tacrolimus), and occasionally rituximab. However, UIP IPAF would result in a more circumspect use of immunosuppression and early evaluation of antifibrotic treatment, particularly when PPF is defined.[77]

Patients who fulfilled IPAF criteria were included in a phase 2 trial of pirfenidone at 2,403 mg/day versus placebo for unclassifiable ILD.[78] There were 12% of patients with IPAF in the pirfenidone arm versus 14% in the placebo arm, and in 5% of both groups, Mycophenolate was used concomitantly. Although results for key secondary endpoints support that pirfenidone treatment slows disease progression, that study[78] has some limitations, because there were some methodological issues in the primary endpoint and in the secondary outcome; IPAF patients presented no statistical difference in FVC change. Regarding nintedanib, a total of 114 patients (17%) in an RCT[23] had unclassifiable ILD; it is unclear how many of them fulfilled IPAF criteria.

Treatment decisions currently need to be made in a multidisciplinary context and based on a thorough assessment of the benefit to determine the risk ratio for each individual patient.

Mixed CTD

Mixed CTD describes a group of systemic autoimmune diseases that share characteristics with one or more than one systemic autoimmune disease. These diseases include RA, SSc, IIM, and SLE. Antibodies against the nuclear ribonucleoprotein autoantigen are thought to be the serological signature of the condition. Pulmonary involvement is a prominent characteristic of mixed CTD; however, most mixed CTD patients remain asymptomatic.

Treatment for ILD-mixed CTD-associated ILD is usually administered based on the predominant overlapping disease feature that presents with stronger evidence. Corticosteroids, mycophenolate, azathioprine, and rituximab are possible options for these patients.[2,79]

ADDITIONAL MANAGEMENT STRATEGIES IN CTD-ILD

A multidisciplinary strategy should be used in the treatment of patients with CTD-ILD. It is crucial to provide assistance with smoking cessation and lung rehabilitation, because these measures could enhance quality of life. Although not formally studied in CTD-ILD, cardiopulmonary rehabilitation is useful for both the ILD component and possible extrathoracic components. The use of oxygen supplementation should be evaluated to ensure that hypoxia is not present at rest, during exercise, or while sleeping.

Vaccination for influenza, pneumococci, COVID-19, pertussis, and herpes zoster should be offered. Also, *Pneumocystis jirovecii* pneumonia prophylaxis should be considered, especially if > 20 mg/day of prednisone or its equivalent are used or if a lower dose is associated with an immunosuppressive drug. Evaluation for latent tuberculosis and other infectious disease (hepatitis B and C, HIV) is advised.[80] Lung transplantation and evaluation for palliative care

should be considered when diseases progress despite treatment (Figure 7).

FINAL CONSIDERATIONS

ILD influences CTD patients' mortality and morbidity. Therefore, effective management is essential for improving survival. The screening and treatment of patients with CTD-ILD are not supported by strong data, with the exception of SSc-ILD. Immunosuppressants are typically the main treatment for CTD-ILD, although there is a lack of data to support the effectiveness or safety of all currently prescribed drugs.

AUTHOR CONTRIBUTIONS

KMS: substantial contributions to study conception/design, and data acquisition, analysis, and interpretation. CSM and MCAP: data acquisition, analysis, and interpretation. KMS and CACP: drafting of the manuscript and critical revision of the manuscript for important intellectual content. All of the authors agreed to be accountable for all aspects of the study, ensuring that questions related to the accuracy and integrity of any part of the study have been appropriately investigated and resolved. All authors read and approved the final version of the manuscript.

Additional therapies
Smoking cessation
Pulmonary rehabilitation
Vaccination
Pneumocystis jirovecii prophylaxis
Evaluation for oxygen supplementation
Evaluation for latent tuberculosis and other infectious diseases
Evaluation for lung transplant
Evaluation for palliative care

Figure 7. Suggested additional therapies for treatment of connective tissue disease-associated interstitial lung disease.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders [published correction appears in Lancet. 2012 Sep 29;380(9848):1148]. Lancet. 2012;380(9842):689-698. https://doi.org/10.1016/S0140-6736(12)61079-4
2. Atzeni F, Gerardi MC, Barilaro G, Masala IF, Benucci M, Sarzi-Puttini P. Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review. Expert Rev Clin Immunol. 2018;14(1):69-82. https://doi.org/10.1080/1744666X.2018.1411190
3. Hunninghake GM, Goldin JG, Kadoch MA, Kropski JA, Rosas IO, Wells AU, et al. Detection and Early Referral of Patients With Interstitial Lung Abnormalities: An Expert Survey Initiative. Chest. 2022;161(2):470-482. https://doi.org/10.1016/j.chest.2021.06.035
4. Smith V, Scirè CA, Talarico R, Airo P, Alexander T, Allanore Y, et al. Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open. 2018;4(Suppl 1):e000782. https://doi.org/10.1136/rmdopen-2018-000782
5. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol. 2020;2(2):e71-e83. https://doi.org/10.1016/S2665-9913(19)30144-4
6. Kawano-Dourado L, Lee JS. Management of Connective Tissue Disease-Associated Interstitial Lung Disease. Clin Chest Med. 2021;42(2):295-310. https://doi.org/10.1016/j.ccm.2021.03.010
7. Roofeh D, Lescoat A, Khanna D. Treatment for systemic sclerosis-associated interstitial lung disease. Curr Opin Rheumatol. 2021;33(3):240-248. https://doi.org/10.1097/BOR.0000000000000795
8. Fischer A, Strek ME, Cottin V, Dellaripa PF, Bernstein EJ, Brown KK, et al. Proceedings of the American College of Rheumatology/Association of Physicians of Great Britain and Ireland Connective Tissue Disease-Associated Interstitial Lung Disease Summit: A Multidisciplinary Approach to Address Challenges and Opportunities. Arthritis Rheumatol. 2019;71(2):182-195. https://doi.org/10.1002/art.40769
9. rang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. Rheumatol Int. 2012;32(3):645-653. https://doi.org/10.1007/s00296-010-1697-6
10. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354(25):2655-2666. https://doi.org/10.1056/NEJMoa055120
11. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-719. https://doi.org/10.1016/S2213-2600(16)30152-7
12. Fernández-Codina A, Walker KM, Pope JE; Scleroderma Algorithm Group. Treatment Algorithms for Systemic Sclerosis According to Experts. Arthritis Rheumatol. 2018;70(11):1820-1828. https://doi.org/10.1002/art.40560
13. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial [published correction appears in Lancet. 2018 Apr 7;391(10128):1356]. Lancet. 2016;387(10038):2630-2640. https://doi.org/10.1016/S0140-6736(16)00232-4
14. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet Respir Med. 2020 Oct;8(10):e75] [published correction appears in Lancet Respir Med. 2021 Mar;9(3):e29]. Lancet Respir Med. 2020;8(10):963-974. https://doi.org/10.1016/S2213-2600(20)30318-0
15. Roofeh D, Lin CJF, Goldin J, Kim GH, Furst DE, Denton CP, et al. Tocilizumab Prevents Progression of Early Systemic Sclerosis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2021;73(7):1301-1310. https://doi.org/10.1002/art.41668
16. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, et al. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. Lancet Rheumatol. 2021;3(7):e489-e497. https://doi.org/10.1016/S2665-9913(21)00107-7
17. Goswami RP, Ray A, Chatterjee M, Mukherjee A, Sircar G, Ghosh P. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. Rheumatology (Oxford). 2021;60(2):557-567. https://doi.org/10.1093/rheumatology/keaa550
18. Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med. 2023;11(1):45-54. https://doi.org/10.1016/S2213-2600(22)00359-9
19. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-1339. https://doi.org/10.1136/annrheumdis-2016-209909
20. Narváez J, LLuch J, Molina-Molina M, Vicens-Zygmunt V, Luburich P, Yañez MA, et al. Rituximab as a rescue treatment added on mycophenolate mofetil background therapy in

progressive systemic sclerosis associated interstitial lung disease unresponsive to conventional immunosuppression. Semin Arthritis Rheum. 2020;50(5):977-987. https://doi.org/10.1016/j.semarthrit.2020.08.004

21. Distler O, Gahlemann M, Maher TM. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. Reply. N Engl J Med. 2019;381(16):1596-1597. https://doi.org/10.1056/NEJMc1910735
22. Khanna D, Maher TM, Volkmann ER, Allanore Y, Smith V, Assassi S, et al. Effect of nintedanib in patients with systemic sclerosis-associated interstitial lung disease and risk factors for rapid progression. RMD Open. 2023;9(1):e002859. https://doi.org/10.1136/rmdopen-2022-002859
23. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-1727. https://doi.org/10.1056/NEJMoa1908681
24. Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, et al. An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial. J Rheumatol. 2016;43(9):1672-1679. https://doi.org/10.3899/jrheum.151322
25. Khanna D, Spino C, Bernstein E, Goldin J, Tashkin D, roth M, SLS III Investigators O. Combination Therapy of Mycophenolate Mofetil and Pirfenidone vs. Mycophenolate Alone: Results from the Scleroderma Lung Study III [abstract]. Arthritis Rheumatol. 2022;74(suppl 9). https://acrabstracts.org/abstract/combination-therapy-of-mycophenolate-mofetil-and-pirfenidone-vs-mycophenolate-alone-results-from-the-scleroderma-lung-study-iii/
26. Raghu G, Montesi SB, Silver RM, Hossain T, Macrea M, Herman D, et al. Treatment of Systemic Sclerosis-associated Interstitial Lung Disease: Evidence-based Recommendations. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2024;209(2):137-152. https://doi.org/10.1164/rccm.202306-1113ST
27. Severo CR, Chomiski C, Valle MBD, Escuissato DL, Paiva EDS, Storrer KM. Assessment of risk factors in patients with rheumatoid arthritis-associated interstitial lung disease. J Bras Pneumol. 2022;48(6):e20220145. https://doi.org/10.36416/1806-3756/e20220145
28. Rodríguez Portal JA, Brito García N, Díaz Del Campo Fontecha P, Valenzuela C, Ortiz AM, Nieto MA, et al. SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 1: Epidemiology, risk factors and prognosis. Reumatol Clin (Engl Ed). 2022;18(8):443-452. https://doi.org/10.1016/j.reuma.2022.02.009
29. Kawassaki AM, Pereira DA, Kay FU, Laurindo IM, Carvalho CR, Kairalla RA. Pulmonary involvement in rheumatoid arthritis: evaluation by radiography and spirometry. J Bras Pneumol. 2015;41(4):331-342. https://doi.org/10.1590/S1806-37132015000004518
30. Koduri G, Solomon JJ. Identification, Monitoring, and Management of Rheumatoid Arthritis-Associated Interstitial Lung Disease. Arthritis Rheumatol. 2023;75(12):2067-2077. https://doi.org/10.1002/art.42640
31. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford). 2017;56(3):344-350. https://doi.org/10.1093/rheumatology/kex299
32. Juge PA, Lee JS, Lau J, Kawano-Dourado L, Rojas Serrano J, Sebastiani M, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J. 2021;57(2):2000337. https://doi.org/10.1183/13993003.00337-2020
33. Kelly C. Lung Disease in Rheumatic Disorders. Mediterr J Rheumatol. 2019;30(3):147-154. https://doi.org/10.31138/mjr.30.3.147
34. Saketkoo LA, Espinoza LR. Rheumatoid arthritis interstitial lung disease: mycophenolate mofetil as an antifibrotic and disease-modifying antirheumatic drug. Arch Intern Med. 2008;168(15):1718-1719. https://doi.org/10.1001/archinte.168.15.1718
35. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40(5):640-646. https://doi.org/10.3899/jrheum.121043
36. Schupp JC, Köhler T, Müller-Quernheim J. Usefulness of Cyclophosphamide Pulse Therapy in Interstitial Lung Diseases. Respiration. 2016;91(4):296-301. https://doi.org/10.1159/000445031
37. Kelly CA, Nisar M, Arthanari S, Carty S, Woodhead FA, Price-Forbes A, et al. Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. Rheumatology (Oxford). 2021;60(4):1882-1890. https://doi.org/10.1093/rheumatology/keaa577
38. Cassone G, Manfredi A, Vacchi C, Luppi F, Coppi F, Salvarani C, et al. Treatment of Rheumatoid Arthritis-Associated Interstitial Lung Disease: Lights and Shadows. J Clin Med. 2020;9(4):1082. https://doi.org/10.3390/jcm9041082
39. Narváez J, Díaz Del Campo Fontecha P, Brito García N, Bonilla G, Aburto M, Castellví I, et al. SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: Treatment. Reumatol Clin (Engl Ed). 2022;18(9):501-512. https://doi.org/10.1016/j.reuma.2022.03.005
40. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613-626. https://doi.org/10.1016/j.semarthrit.2013.09.005
41. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41(1):15-23. https://doi.org/10.3899/jrheum.130466
42. Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. Intern Med J. 2020;50(9):1085-1090. https://doi.org/10.1111/imj.14670
43. Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. Rheumatol Int. 2016;36(6):881-889. https://doi.org/10.1007/s00296-016-3478-3
44. Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of Abatacept in Italian Patients with Rheumatoid Arthritis and Interstitial Lung Disease: A Multicenter Retrospective Study. J Clin Med. 2020;9(1):277. https://doi.org/10.3390/jcm9010277
45. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. Arthritis Res Ther. 2015;17:319. https://doi.org/10.1186/s13075-015-0835-7
46. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary [published correction appears in Rheumatology (Oxford). 2019 Feb 1;58(2):372]. Rheumatology (Oxford). 2019;58(2):220-226. https://doi.org/10.1093/rheumatology/key207
47. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford). 2017;56(8):1348-1357. https://doi.org/10.1093/rheumatology/kex072
48. Fui A, Bergantini L, Selvi E, Mazzei MA, Bennett D, Pieroni MG, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. Intern Med J. 2020;50(3):330-336. https://doi.org/10.1111/imj.14306
49. Duarte AC, Porter JC, Leandro MJ. The lung in a cohort of rheumatoid arthritis patients-an overview of different types of involvement and treatment. Rheumatology (Oxford). 2019;58(11):2031-2038. https://doi.org/10.1093/rheumatology/kez177
50. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010;62(9):2625-2632. https://doi.org/10.1002/art.27555
51. Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir Med. 2023;11(1):87-96. https://doi.org/10.1016/S2213-2600(22)00260-0
52. Wang J, Wang X, Qi X, Sun Z, Zhang T, Cui Y, et al. The Efficacy and Safety of Pirfenidone Combined With Immunosuppressant Therapy in Connective Tissue Disease-Associated Interstitial Lung Disease: A 24-Week Prospective Controlled Cohort Study. Front Med (Lausanne). 2022;9:871861. https://doi.org/10.3389/fmed.2022.871861
53. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical

Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-e47. https://doi.org/10.1164/rccm.202202-0399ST

54. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. 2017 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups [published correction appears in Ann Rheum Dis. 2018 Sep;77(9):e64]. Ann Rheum Dis. 2017;76(12):1955-1964. https://doi.org/10.1136/annrheumdis-2017-211468
55. Barba T, Mainbourg S, Nasser M, Lega JC, Cottin V. Lung Diseases in Inflammatory Myopathies. Semin Respir Crit Care Med. 2019;40(2):255-270. https://doi.org/10.1055/s-0039-1685187
56. Chung JH, Cox CW, Montner SM, Adegunsoye A, Oldham JM, Husain AN, et al. CT Features of the Usual Interstitial Pneumonia Pattern: Differentiating Connective Tissue Disease-Associated Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis. AJR Am J Roentgenol. 2018;210(2):307-313. https://doi.org/10.2214/AJR.17.18384
57. Barba T, Fort R, Cottin V, Provencher S, Durieu I, Jardel S, et al. Treatment of idiopathic inflammatory myositis associated interstitial lung disease: A systematic review and meta-analysis. Autoimmun Rev. 2019;18(2):113-122. https://doi.org/10.1016/j.autrev.2018.07.013
58. harma N, Putman MS, Vij R, Strek ME, Dua A. Myositis-associated Interstitial Lung Disease: Predictors of Failure of Conventional Treatment and Response to Tacrolimus in a US Cohort. J Rheumatol. 2017;44(11):1612-1618. https://doi.org/10.3899/jrheum.161217
59. Morisset J, Johnson C, Rich E, Collard HR, Lee JS. Management of Myositis-Related Interstitial Lung Disease. Chest. 2016;150(5):1118-1128. https://doi.org/10.1016/j.chest.2016.04.007
60. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest. 2006;130(1):30-36. https://doi.org/10.1016/S0012-3692(15)50949-5
61. Ge Y, Peng Q, Zhang S, Zhou H, Lu X, Wang G. Cyclophosphamide treatment for idiopathic inflammatory myopathies and related interstitial lung disease: a systematic review. Clin Rheumatol. 2015;34(1):99-105. https://doi.org/10.1007/s10067-014-2803-z
62. Keir GJ, Maher TM, Ming D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology. 2014;19(3):353-359. https://doi.org/10.1111/resp.12214
63. Andersson H, Sem M, Lund MB, Aaløkken TM, Günther A, Walle-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology (Oxford). 2015;54(8):1420-1428. https://doi.org/10.1093/rheumatology/kev004
64. Sharp C, McCabe M, Dodds N, Edey A, Mayers L, Adamali H, et al. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease. Rheumatology (Oxford). 2016;55(7):1318-1324. https://doi.org/10.1093/rheumatology/kew195
65. Doyle TJ, Dhillon N, Madan R, Cabral F, Fletcher EA, Koontz DC, et al. Rituximab in the Treatment of Interstitial Lung Disease Associated with Antisynthetase Syndrome: A Multicenter Retrospective Case Review. J Rheumatol. 2018;45(6):841-850. https://doi.org/10.3899/jrheum.170541
66. Chen Z, Wang X, Ye S. Tofacitinib in Amyopathic Dermatomyositis-Associated Interstitial Lung Disease. N Engl J Med. 2019;381(3):291-293. https://doi.org/10.1056/NEJMc1900045
67. Manfredi A, Sebastiani M, Cerri S, Cassone G, Bellini P, Casa GD, et al. Prevalence and characterization of non-sicca onset primary Sjögren syndrome with interstitial lung involvement [published correction appears in Clin Rheumatol. 2017 Aug;36(8):1931]. Clin Rheumatol. 2017;36(6):1261-1268. https://doi.org/10.1007/s10067-017-3601-1
68. Lee AS, Scofield RH, Hammitt KM, Gupta N, Thomas DE, Moua T, et al. Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's. Chest. 2021;159(2):683-698. https://doi.org/10.1016/j.chest.2020.10.011
69. Kreider M, Highland K. Pulmonary involvement in Sjögren syndrome. Semin Respir Crit Care Med. 2014;35(2):255-264. https://doi.org/10.1055/s-0034-1371529
70. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest. 2006;130(5):1489-1495. https://doi.org/10.1378/chest.130.5.1489
71. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X. Primary Sjogren syndrome. BMJ. 2012;344:e3821. https://doi.org/10.1136/bmj.e3821
72. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976-987. https://doi.org/10.1183/13993003.00150-2015
73. Graney BA, Fischer A. Interstitial Pneumonia with Autoimmune Features. Ann Am Thorac Soc. 2019;16(5):525-533. https://doi.org/10.1513/AnnalsATS.201808-565CME
74. Oldham JM, Adegunsoye A, Valenzi E, Lee C, Witt L, Chen L, et al. Characterisation of patients with interstitial pneumonia with autoimmune features [published correction appears in Eur Respir J. 2017 May 11;49(5):]. Eur Respir J. 2016;47(6):1767-1775. https://doi.org/10.1183/13993003.01565-2015
75. Chung JH, Montner SM, Adegunsoye A, Lee C, Oldham JM, Husain AN, et al. CT Findings, Radiologic-Pathologic Correlation, and Imaging Predictors of Survival for Patients With Interstitial Pneumonia With Autoimmune Features. AJR Am J Roentgenol. 2017;208(6):1229-1236. https://doi.org/10.2214/AJR.16.17121
76. Ito Y, Arita M, Kumagai S, Takei R, Noyama M, Tokioka F, et al. Serological and morphological prognostic factors in patients with interstitial pneumonia with autoimmune features. BMC Pulm Med. 2017;17(1):111. https://doi.org/10.1186/s12890-017-0453-z
77. Mackintosh JA, Wells AU, Cottin V, Nicholson AG, Renzoni EA. Interstitial pneumonia with autoimmune features: challenges and controversies. Eur Respir Rev. 2021;30(162):210177. https://doi.org/10.1183/16000617.0177-2021
78. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8(2):147-157. https://doi.org/10.1016/S2213-2600(19)30341-8
79. Perelas A, Arrossi AV, Highland KB. Pulmonary Manifestations of Systemic Sclerosis and Mixed Connective Tissue Disease. Clin Chest Med. 2019;40(3):501-518. https://doi.org/10.1016/j.ccm.2019.05.001
80. Dias VL, Storrer KM. Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression. J Bras Pneumol. 2022;48(2):e20210382. https://doi.org/10.36416/1806-3756/e20210382

Rheumatoid arthritis-associated airway disease: longitudinal pulmonary function behavior

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TO THE EDITOR,

Rheumatoid Arthritis-associated airway disease (RA-AWD) is a commonly overlooked pulmonary manifestation of Rheumatoid Arthritis (RA).[1] Its prevalence varies widely, from 8 to 60%, depending on the source of the cases (hospital-based studies or autopsy) and the criteria used to define RA-AWD, whether based on symptoms, pulmonary function tests (PFTs), or imaging.[1]

The spectrum of manifestations ranges from small (bronchiolar) to large airway disease.[2] Despite its high prevalence and complexity, there are few studies in the literature characterizing RA-AWD, and even fewer evaluating its longitudinal course.[3]

In the present study, we describe the longitudinal behavior of PFTs in patients with RA-AWD. This single-center retrospective study involved subjects aged 18 years or older, diagnosed with RA-AWD at a tertiary pulmonary clinic, that were followed between 2016 and 2017. RA-AWD was defined by the absence of interstitial lung disease (ILD) and the presence of features of airway disease on high-resolution computed tomography (HRCT) of the chest, not explained by other diagnoses, such as asthma or COPD. Since smoking is in the causal pathway of RA and likely in the causal pathway of RA-AWD, it was not used as an exclusion criterion.[2]

In order to be considered eligible, patients were required to have undergone a chest HRCT and PFTs. Baseline PFTs were defined as the earliest PFT within a 6-month interval since the HRCT. Up to four additional PFT results were retrieved from the electronic health records (EHR) for estimating the rate of change in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. Clinical data were obtained from the EHR. This project received institutional review board approval from the Clinics Hospital's ethics committee (Process No. 2.825.510).

The earliest available chest HRCT was qualitatively analyzed by two independent readers (LKD and MVYS) for the presence of RA-AWD. Inconsistencies were resolved through consensus (kappa agreement between readers: 0.71).

Imaging findings of RA-AWD were categorized as follows: unequivocal bronchial thickening, mosaic attenuation, centrilobular micronodules, and/or focal or multifocal bronchiectasis.

The annual rate of change in FEV_1, FVC, and the FEV_1/FVC ratio were estimated using a mixed regression model (random slopes and intercepts), including age, sex, and baseline FEV_1, FVC, and FEV_1/FVC (respectively) as covariates. The R Statistical Package was used in the analysis.

Among the 2,495 patients who underwent a follow-up visit at our pulmonary clinic between 2016 and 2017, 96 (3.8%) matched our case definition for RA and pulmonary involvement. Forty-eight out of these 96 (50%) subjects fulfilled the criteria for RA-AWD. The majority of individuals with seropositive RA were females in their sixth decade of life, and the mean disease duration was 15 years. Approximately half of the RA-AWD subjects (48%) had never smoked. No differences were observed between RA-AWD and Rheumatoid Arthritis Interstitial Lung Disease (RA-ILD) regarding previous tuberculosis (TB) contact or treatment for latent TB.[4] Additional clinical variables are shown in Table 1.

The most common HRCT findings among the RA-AWD patients were unequivocal bronchial thickening in 46 (96%), followed by mosaic attenuation in 30 (63%), centrilobular micronodules in 28 (58%), and focal or multifocal bronchiectasis in 23 (48%).

Forty-four patients had at least two PFTs included in the longitudinal analysis. The median interval between the first and last PFTs analyzed was 20 months [IQR: 9.3 – 22.5]. The mean baseline FVC was 79 ± 19% of the predicted value, FEV_1 was 65 ± 22% of the predicted value, and the FEV_1/FVC ratio was 0.65 ± 0.17, characterizing a mild obstructive ventilatory defect (OVD) (Table 1). A statistically significant annual decline in FVC was observed (-1.45% predicted, 95% CI: -2.37 to -0.53), while the FEV_1 remained stable (-0.62% predicted, 95% CI: -1.54 to 0.30), leading

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Table 1. Baseline characteristics of patients with rheumatoid arthritis-associated airway disease (RA-AWD).

Characteristics	RA-AWD n = 48 (50%)
Age in years, mean (SD)	62 (11)
Females, n. (%)	43 (90%)
RA disease duration in years, mean (SD)	15 (10)
RF positivity, n. (%)	36 (78%)
RF titer, mean in IU/mL (SD)	166 (141)
ACPA positivity, n. (%)	10 (71%) n = 14
ACPA titer (IU/mL)	163 (70)
Ever smokers, n. (%)	25 (52%)
Asthma, n. (%)	6 (15%) n = 39
COPD, n. (%)	8 (20%) n = 39
Sjögren Syndrome, n. (%)	3 (8%) n = 39
Latent TB treatment, n. (%)	5 (10%)
Past history of treated TB, n. (%)	4 (8%)
Environmental exposures, n. (%)	
Avian antigen	14 (61%)
Wood burning	8 (35%)
Mold	8 (35%)
Metal processing industry	1 (4%)
Comorbidities, n. (%)	
Arterial hypertension	19 (58%)
Hypothyroidism	13 (39%)
Ischemic heart disease	8 (24%)
Dyslipidemia	6 (18%)
Diabetes mellitus	6 (18%)
Previous treatments for RA[§], n. (%)	
Prednisone	32 (67%)
Methotrexate	30 (63%)
Leflunomide	24 (50%)
Biologic and/or targeted synthetic DMARDs	13 (25%)
Airway HRCT findings, n. (%)[§§]	
Bronchial wall thickening	46 (96%)
Mosaic attenuation	30 (63%)
Centrilobular micronodules	28 (58%)
Focal or multifocal bronchiectasis	23 (48%)
Baseline Pulmonary Function Test	
FVC, L (SD)	2.25 ± 0.62
FVC, % of predicted	79 ± 19%
FEV_1, L (SD)	1.46 ± 0.53
FEV_1, % of predicted	65 ± 22%
FEV_1/FVC ratio	0.65 ± 0.17

Abbreviations: RA-AWD: rheumatoid arthritis-associated airway disease; SD: standard deviation; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; TB: Tuberculosis; DMARDS: disease-modifying antirheumatic drugs; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; NA: not available; HRCT: high-resolution computed tomography. [§]Use at any time for longer than 3 months until first chest HRTC. [§§]Proportion of cases presenting the image finding. One case may present more than one finding.

to a statistically significant increase in the FEV_1/FVC ratio of 0.01 (95% CI: 0.005 to 0.016), suggesting air trapping and/or hyperinflation (Figure 1).

As expected for a sample of RA patients, half of the subjects had been exposed to tobacco. Excluding patients with a smoking history from the analyses would likely bias the results, as smoking is in the direct causal pathway of RA itself.[5] Functionally, one case of mild OVD evolved with FVC reduction and an increase in the FEV_1/FVC ratio, suggesting air trapping/hyperinflation, replicating previous longitudinal findings in RA-AWD.[3] Of note, the estimation of air trapping/hyperinflation by the FEV_1/FVC ratio is considered accurate when compared to the residual volume/total lung capacity ratio.[6] In COPD, air trapping/hyperinflation is associated with an increased risk of

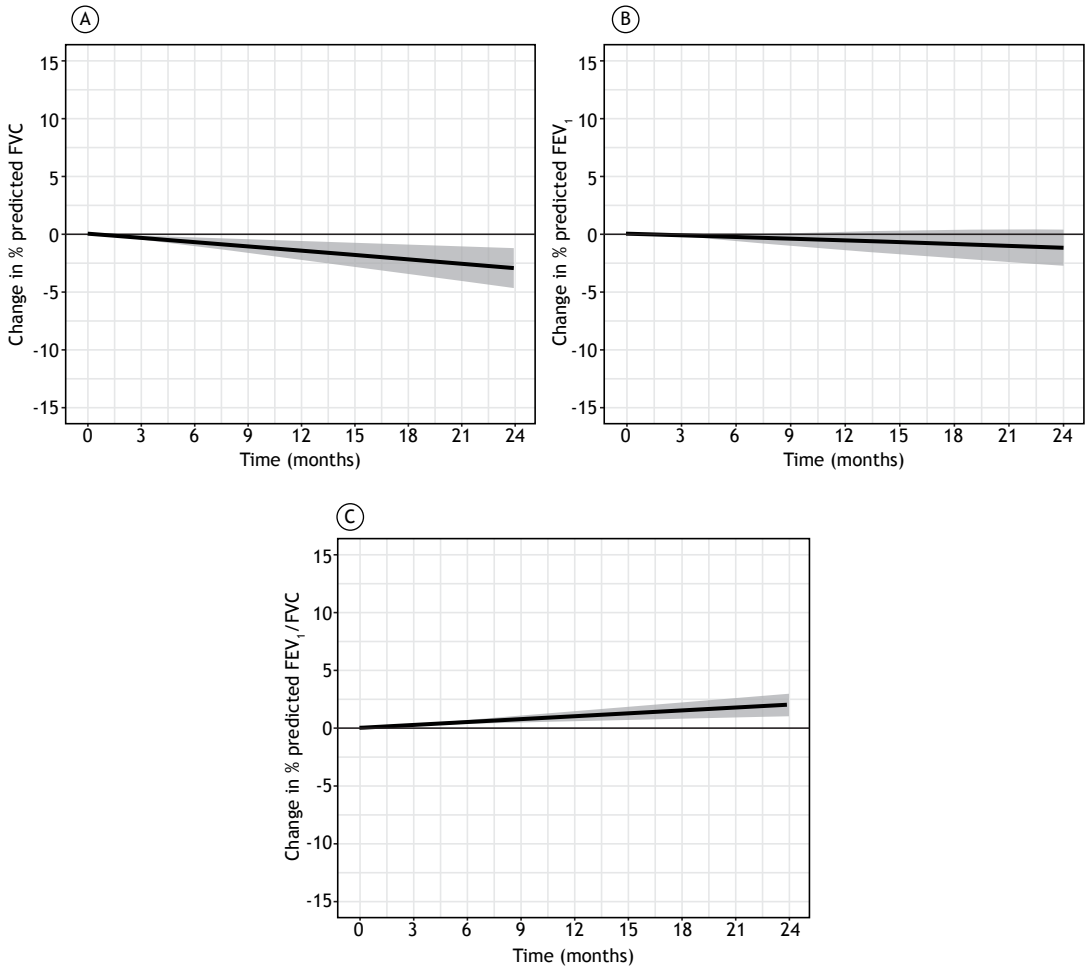

Figure 1. Longitudinal pulmonary function test behavior among rheumatoid arthritis-associated airway disease (RA-AWD) cases. (A) Change in % predicted in forced vital capacity (FVC). (B) Change in % predicted in the forced expiratory volume in one second (FEV1). (C) Change in % predicted FEV1/FVC ratio. The grey shadow represents the 95% confidence interval (95% CI).

disease exacerbation, a higher degree of dyspnea, and a poorer quality of life. While these aspects were not assessed in our study, they should serve as plausible research hypotheses to be investigated in RA-AWD.[7]

The tomographic findings observed in this study are consistent with what has been previously described.[2] Additionally, despite this cohort originating from an endemic region for TB, the proportions of bronchiectasis and bronchial wall thickening (common TB sequelae) found in our sample were similar to previous reports on RA-AWD from non-endemic TB regions.[8,9]

This study had some limitations. Firstly, it was a retrospective single-center study. Nevertheless, our sample characteristics are similar to previous RA-AWD reports in the literature.[1,2,3,9] Secondly, data on HRCT follow-up were unavailable. On the other hand, our study thoroughly characterized the baseline HRCT findings and the longitudinal PFT behaviour in RA-AWD subjects, suggesting air trapping/hyperinflation as an important mechanism of disease progression. Patients self-reported environmental exposure avoidance and smoking cessation; hence, these factors are unlikely to be the causal determinants of our functional longitudinal findings. A past history of tuberculosis treatment was present in only 8% of our sample, and the removal of these patients did not alter the results (data not shown).

In conclusion, in the present cohort, RA-AWD was characterized by small and large airway imaging findings that were associated with an obstructive ventilatory defect. During follow-up, the observed increase in air trapping and/or hyperinflation potentially accounted for the reduction in FVC and the increase in the FEV_1/FVC ratio. Additional studies are warranted to confirm air trapping/hyperinflation as a mechanism of progression in RA-AWD, which, in turn, may impact the choice of interventions to be tested in the management of this condition.

AUTHOR CONTRIBUTIONS

The authors confirmed contribution to the paper as follows: study conception and design MLBS, CAM, MVYS,

KB, RAK, BGB, LKD; data collection MLBS, CAM, FEA, LKD; analysis and interpretation of results MLBS, CAM, AP, RHN, RAA, BGB, LKD; draft manuscript preparation MLBS, CAM, MVYS, KB, ACMR, AP, RHN, FEA, RAA, RAK, BGB, LKD. All authors reviewed the results and approved the final version of the manuscript. Both MLBS and LKD contributed equally.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Matson SM, Demoruelle MK, Castro M. Airway Disease in Rheumatoid Arthritis. Ann Am Thorac Soc. 2022 Mar;19(3):343-52. https://doi.org/10.1513/AnnalsATS.202107-876CME.
2. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1658-65. https://doi.org/10.1164/ajrccm.157.5.9710018.
3. Fuld JP, Johnson MK, Cotton MM, Carter R, Watkin SW, Capell HA, et al. A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis. Chest. 2003;124(4):1224-31. https://doi.org/10.1378/chest.124.4.1224.
4. Sabbag ML, Molina C de Assis, Sawamura M, Bonfiglioli K, Arimura FE, Athanazio RA et al. Characterization of Airway Disease in Rheumatoid Arthritis. Am J Resp Crit Care Med 2019; 199:A1440. Disponível em: <https://observatorio.fm.usp.br/handle/OPI/32693>.
5. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006 Jan;54(1):38-46. https://doi.org/10.1002/art.21575.
6. Alter P, Orszag J, Kellerer C, Kahnert K, Speicher T, Watz H, et al. Prediction of air trapping or pulmonary hyperinflation by forced spirometry in COPD patients: results from COSYCONET. ERJ Open Res. 2020 Jul;6(3):00092-2020; https://doi.org/10.1183/23120541.00092-2020.
7. Kim Y, Kim SH, Rhee CK, Lee JS, Lee CY, Kim DK, et al. Air Trapping and the Risk of COPD Exacerbation: Analysis From Prospective KOCOSS Cohort. Front Med (Lausanne). 2022 Mar;9:835069. https://doi.org/10.3389/fmed.2022.835069.
8. Kronzer VL, Westerlind H, Alfredsson L, Crowson CS, Nyberg F, Tornling G, et al. Respiratory Diseases as Risk Factors for Seropositive and Seronegative Rheumatoid Arthritis and in Relation to Smoking. Arthritis Rheumatol. 2021 Jan;73(1):61-8. https://doi.org/10.1002/art.41491.
9. Vuorela M, Mars NJ, Salonen J, Kauppi MJ. Tuberculosis in people with rheumatic disease in Finland 1995–2007: a nationwide retrospective register study. Rheumatol Adv Pract. 2019 Aug;3(2):rkz020. https://doi.org/10.1093/rap/rkz020.

Bullous emphysema in a cannabis user

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

A 48-year-old man presented with progressive dyspnea for 2 years that had been worsening for one month, preventing daily activities. His oxygen saturation was 88%. He had a history of active, daily, heavy marijuana smoking for the last 30 years and no history of tobacco use. Chest CT showed large emphysematous bullae predominating in the upper fields of the lungs, the largest one in the right lung. The patient was later referred for surgical bullectomy. His bullous emphysema was attributed to heavy cannabis use.

Cannabis is the most widely used illicit drug in the world and the second most commonly smoked substance after tobacco. The specific effects of cannabis smoking are subject to confounding by concomitant tobacco use, although the pathological changes occur approximately 20 years earlier than in tobacco smokers. Cannabis is usually smoked without a filter, and users inhale larger volumes with longer breath holds when compared with tobacco smokers. Such usage may cause increased intra-alveolar pressure with significant barotrauma. Paraseptal emphysema may represent an early stage of apical bulla formation. Affected patients are predisposed to the development of bullous emphysema, pneumothorax, and pneumomediastinum. Other thoracic complications, such as lung cancer, myocardial infarction, and alveolar hemorrhage, are less common.[1-3]

AUTHOR CONTRIBUTIONS

All of the authors equally contributed to reviewing the literature, analyzing the images, writing and reviewing of the manuscript, and approving the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare having no conflicts of interest to express.

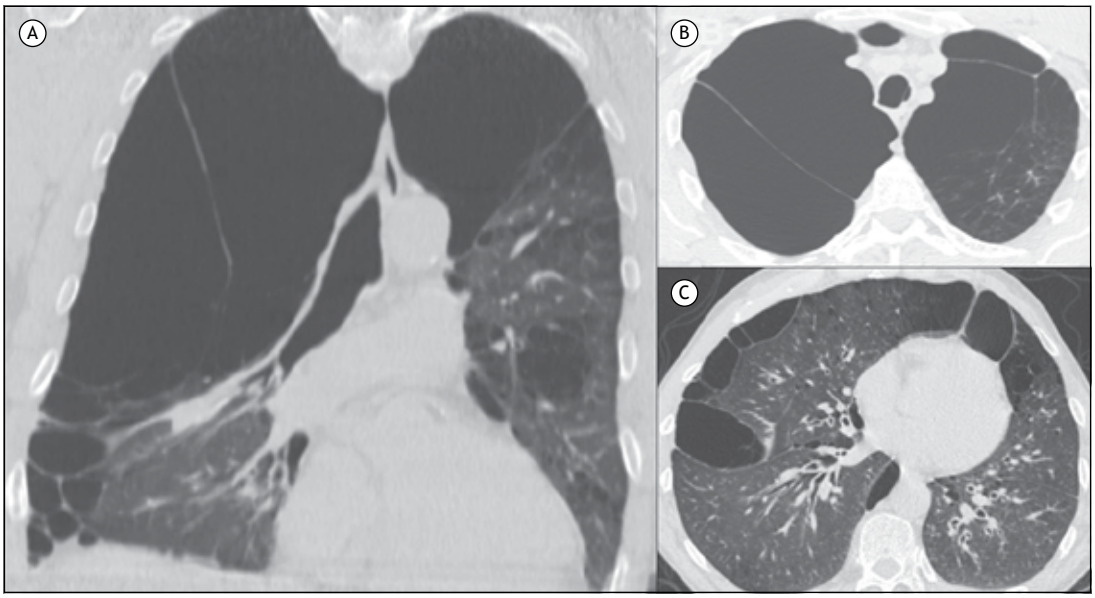

Figure 1. Chest CT scans with coronal (A) and axial (B and C) reconstructions showing large emphysematous bullae predominating in the upper fields of the lungs, the largest one in the right lung.

REFERENCES

1. Murtha L, Sathiadoss P, Salameh JP, Mcinnes MDF, Revah G. Chest CT Findings in Marijuana Smokers. Radiology. 2023;307(1):e212611. https://doi.org/10.1148/radiol.212611
2. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. Curr Opin Pulm Med 2014;20(2):173-179. https://doi.org/10.1097/MCP.0000000000000026
3. Vásconez-González J, Delgado-Moreira K, López-Molina B, Izquierdo-Condoy JS, Gámez-Rivera E, Ortiz-Prado E. Effects of Smoking Marijuana on the Respiratory System: A Systematic Review. Subst Abus. 2023;44(3):249-260. https://doi.org/10.1177/08897077231186228

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Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

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Referências:

1. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017 Aug 3;50(2):1700889. 2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. 3. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017 Aug 3;50(2):1700740. 4. Delcroix M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2018 Nov 8;52(5):1800248. 5. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019 Aug;156(2):323-337. 6. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension. Chest. 2021 Jan;159(1):337-346.

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A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. 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Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

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