ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 48, Number 6
November | December
2022

Volume 48, Number 6 November | December 2022

HIGHLIGHT

Relationship between wheezing and obesity in adolescence and young adulthood

Interstitial lung disease associated with rheumatoid arthritis

Predictive factors for obstructive sleep apnea in obese patients referred for bariatric surgery

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

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

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

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

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

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

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

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
MP 05.2020 - Junho 2020.

moksha8

ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 6, November/December 2022

Associação Brasileira de Editores Científicos ABEC

Publicação Indexada em:
Latindex, LILACS, Scielo Brazil, Scopus, Index Copernicus, ISI Web of Knowledge, MEDLINE e PubMed Central (PMC)

Disponível eletronicamente nas versões português e inglês:
www.jornaldepneumologia.com.br e www.scielo.br/jbpneu

NATIONAL LIBRARY OF MEDICINE

PMC

ISI Web of Knowledge℠

SCOPUS

SciELO Brazil

INDEX COPERNICUS INTERNATIONAL

latindex

ISSN (ON-LINE): 1806-3756

Expediente

Jornal Brasileiro de Pneumologia

BRAZILIAN THORACIC SOCIETY

Office: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218. Website: www.sbpt.org.br.
E-mail: sbpt@sbpt.org.br

The Brazilian Journal of Pulmonology (ISSN 1806-3756) is published once every two months by the Brazilian Thoracic Society (BTS). The statements and opinions contained in the editorials and articles in this Journal are solely those of the authors thereof and not of the Journal's Editor-in-Chief, peer reviewers, the BTS, its officers, regents, members, or employees. Permission is granted to reproduce any figure, table, or other material published in the Journal provided that the source for any of these is credited.

ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Distribution: Free to members of the BTS and libraries

SUPPORT:
CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES
Ministério da Educação
Ministério da Ciência, Tecnologia e Inovação
GOVERNO FEDERAL BRASIL PAÍS RICO É PAÍS SEM POBREZA

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 6, November/December 2022

Contents

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 6, November/December 2022

Contents

J Bras Pneumol. 2022;48(6):20220429
https://dx.doi.org/10.36416/1806-3756/20220429

Repercussions of the COVID-19 pandemic for science and for the management of the *Jornal Brasileiro de Pneumologia*

Bruno Guedes Baldi[1,2,3], Marcia Margaret Menezes Pizzichini[4,5]

Since the WHO declared infection with the novel coronavirus (COVID-19) to be a pandemic, on March 11, 2022, there have been unprecedented relevant developments in various areas, including health, politics, economics, and science.[1] Although the number of cases of COVID-19 and COVID-19-related deaths has decreased significantly over the last year, the short- and long-term impacts of the pandemic have been impressive. Worldwide, there have been more than 626 million cases of COVID-19, resulting in more than 6.56 million deaths; in Brazil alone, more than 34.8 million cases have been reported and there have been more than 687,000 COVID-19-related deaths.[2] Pulmonary involvement was and continues to be the leading cause of hospitalization and death among patients with COVID-19.[2,3]

Over a short period of time, there were dramatic advances in the science related to COVID-19, those advances representing a determining factor for the control of the pandemic, with progressive reductions in the number of cases, the severity of those cases, and the number of deaths.[4,5] Due to the urgency of the situation and the significant increase in the number of submissions, there was a need to respond rapidly to all of the challenges, which presented themselves in an accelerated manner.[4,6] On November 1, 2022, PubMed searches for "COVID" and for "COVID" AND "Brazil" identified 304,207 and 9,497 manuscripts, respectively.[7,8] Various strategies were essential to meet the demand in the management of journals during COVID-19, including those related to the field of respiratory medicine, with the objective of streamlining the process for each manuscript, from its submission through the steps of editorial review, peer review, editing, revision, publication, and dissemination.[5,9] In this context, it is important to highlight the arduous and remarkable work of the editorial teams and reviewers of journals in the area of respiratory medicine during the pandemic. Other relevant advances resulting from the COVID-19 pandemic include the expansion of national and international research partnerships, the development and structuring of research centers, and open access to published articles on the topic, a fundamental aspect of providing universal access to information.

For journals focusing on pulmonary and respiratory medicine, the significant impact on the number of submissions was accompanied by a significant increase in the number of citations of COVID-19-related articles, which certainly explains, in part, the fact that the impact factors (IFs) of many such journals increased in 2022, as evidenced in the Journal Citation Reports database maintained by Clarivate Analytics.[10] The question is whether the effects of COVID-19 on the IFs of journals will persist for a prolonged period of time. It is important to remain attentive to the quality and relevance of submissions, including those related to long COVID, as well as to the number of citations.

There are some unfavorable aspects of the scientific production related to COVID-19. There has been an excessive number of published articles on COVID-19 in all fields, including that of respiratory medicine. Many articles have not presented consistent novel findings, rather reproducing those of previous studies; others have been of poor scientific quality, whereas others were case reports or case series.[4,6] In addition, the rush to publish articles on the topic might have created a risk of reducing the scientific rigor in their evaluation, resulting in lower scientific quality of some articles.[5,9] There was also a need to publish errata and retractions of some manuscripts because of methodological problems related to databases and results.[5,11,12] Therefore, it is essential to stand firm against the pressure to publish without adopting rigid criteria in all steps of the editorial process, even in situations of epidemiological urgency. In addition to the obvious scientific repercussions, it should be emphasized that the publication of articles related to the pandemic can have an impact on the implementation of public policies in various areas, especially in the area of health care. Another noteworthy difficulty faced by many journals, including the *Jornal Brasileiro de Pneumologia* (JBP), was that of finding reviewers, mainly due to the large volume of articles submitted. There has also been much discussion regarding the overall difficulty of properly recognizing and valuing the work of reviewers, in order to make the act of reviewing articles more attractive. Another negative aspect is the intense pressure that many researchers felt to publish studies during the pandemic, mainly due to greater competitiveness, which might have caused anguish and resulted in burnout, generating an exacerbated feeling of frustration among those who failed to publish.[13]

The repercussions of COVID-19 for the JBP were also quite significant. From the beginning of the pandemic until November 1, 2022, 1,453 manuscripts were submitted to the JBP, of which 365 (25.1%) were about COVID-19. The overall rejection rate for articles submitted to the JBP during that period was 73%, reaching 80% for those with a COVID-19 theme. The turnaround time between the submission of an article and the initial decision of the

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clinicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.
2. Editor-Chefe do Jornal Brasileiro de Pneumologia, Brasília (DF) Brasil.
3. Hospital do Coração, São Paulo (SP) Brasil
4. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
5. Vice-Editora do Jornal Brasileiro de Pneumologia, Brasília (DF) Brasil.

editor was reduced from 30 days to 23 days during the COVID-19 pandemic. During the pandemic, 384 articles were published in the JBP, of which 75 (19.5%) were on the topic of COVID-19. Among the COVID-19-related articles published, the top three article types were letters to the editor (29.3%), editorials (25.3%), and original articles (20.0%). The three most cited articles on COVID-19 in the JBP received 23, 18, and 15 citations, respectively.[14-16] The IF of the JBP has shown progressive growth in recent years in the Clarivate Analytics Journal Citation Reports database, reaching 2.800 in 2022. Citations related to articles on COVID-19 were the most frequent, accounting for 19.5% of the total for the IF in question, compared with only 14.0% for those related to articles on tuberculosis.[10]

Although strategies for the management of the JBP, including the modification of editorial processes, were adopted during the COVID-19 pandemic, scientific rigor in the evaluation of manuscripts was always maintained. We sought to reduce the time for the evaluation of manuscripts in order to speed their publication after approval, and the continuous publication modality adopted in recent years was fundamental for achieving that goal. The dissemination of COVID-19-related articles on various social networks and on the JBP website was expanded, and a specific area for manuscripts on the topic was created on the Journal website. The lead authors of featured articles on COVID-19 recorded podcasts and provided abstracts for the dissemination of those articles. The authors of some original articles were asked to resubmit them as letters to the editor, and the number of editorials on COVID-19, especially those related to "hot topics", was expanded. The articles on COVID-19 submitted to the JBP varied in quality. Some were confirmatory studies that presented results similar to those published in other manuscripts, therefore being of little interest to the Journal. The editorial board played a fundamental role in the initial evaluation of articles on COVID-19 submitted to the JBP, acting in a timely manner in view of the need for a rapid response. The difficulty in finding reviewers for some articles is also noteworthy, underscoring the importance of the strategy adopted by the JBP of expanding the pool of reviewers to include researchers who are at the beginning of their careers but already have some experience in the area. Practices adopted by the JBP to compensate reviewers for their work include extending invitations to write editorials and including their names in acknowledgments, as well as in the list of reviewers released annually and in the credits published on the Publons platform.

Finally, we must thank all of the authors, reviewers, editorial board members, and staff, as well as the board of directors of the *Sociedade Brasileira de Pneumologia e Tisiologia*, who were fundamental for the excellent progress and evolution of the management of the JBP, especially in view of all of the challenges posed by the COVID-19 pandemic. We sought to maintain the JBP as a journal that prioritizes clinical aspects, together with aspects of the practice of pulmonologists and of health care professionals working in related areas, including COVID-19, as well as seeking to improve the quality of articles, thus contributing to scientific advances in the area and to greater internationalization of the Journal.

REFERENCES

1. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2022 [updated 2020 Mar 13; cited 2022 Nov 1]. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020
2. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2022 [updated 2022 Oct 28; cited 2022 Oct 28]. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int/
3. Tanni SE, Fabro AT, de Albuquerque A, Ferreira EVM, Verrastro CGY, Sawamura MVY, et al. Pulmonary fibrosis secondary to COVID-19: a narrative review. Expert Rev Respir Med. 2021;15(6):791-803. https://doi.org/10.1080/17476348.2021.1916472
4. Raynaud M, Goutaudier V, Louis K, Al-Awadhi S, Dubourg Q, Truchot A, et al. Impact of the COVID-19 pandemic on publication dynamics and non-COVID-19 research production. BMC Med Res Methodol. 2021;21(1):255. https://doi.org/10.1186/s12874-021-01404-9
5. Schonhaut L, Costa-Roldan I, Oppenheimer I, Pizarro V, Han D, Díaz F. Scientific publication speed and retractions of COVID-19 pandemic original articles. Rev Panam Salud Publica. 2022;46:e25. https://doi.org/10.26633/RPSP.2022.25
6. Khatter A, Naughton M, Dambha-Miller H, Redmond P. Is rapid scientific publication also high quality? Bibliometric analysis of highly disseminated COVID-19 research papers. Learn Publ. 2021;34(4):568-577. https://doi.org/10.1002/leap.1403
7. National Library of Medicine. PubMed.gov [homepage on the Internet] Bethesda: National Library of Medicine; c2022 [cited 2022 Nov 1]. Search: COVID and Brazil. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=COVID+AND+Brazil&sort=date
8. National Library of Medicine. PubMed.gov [homepage on the Internet] Bethesda: National Library of Medicine; c2022 [cited 2022 Nov 1]. Search: COVID. Available from https://pubmed.ncbi.nlm.nih.gov/?term=COVID&sort=date
9. Putman MS, Ruderman EM, Niforatos JD. Publication Rate and Journal Review Time of COVID-19-Related Research. Mayo Clin Proc. 2020;95(10):2290-2291. https://doi.org/10.1016/j.mayocp.2020.08.017
10. Clarivate. Journal Citation Reports [homepage on the Internet]. c2022 [cited 2022 Nov 1]. Browse journals. Available from https://jcr.clarivate.com/jcr/browse-journals
11. Clarification of Mortality Rate and Data in Abstract, Results, and Table 2. JAMA. 2020;323(20):2098. https://doi.org/10.1001/jama.2020.7681
12. Mehra MR, Ruschitzka F, Patel AN. Retraction-Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [retraction of: Lancet. 2020 May 22;:]. Lancet. 2020;395(10240):1820. https://doi.org/10.1016/S0140-6736(20)31324-6
13. Suart C, Neuman K, Truant R. The impact of the COVID-19 pandemic on perceived publication pressure among academic researchers in Canada. PLoS One. 2022;17(6):e0269743. https://doi.org/10.1371/journal.pone.0269743
14. Araujo-Filho JAB, Sawamura MVY, Costa AN, Cerri GG, Nomura CH. COVID-19 pneumonia: what is the role of imaging in diagnosis?. J Bras Pneumol. 2020;46(2):e20200114. https://doi.org/10.36416/1806-3756/e20200114
15. Baratella E, Crivelli P, Marrocchio C, Bozzato AM, Vito A, Madeddu G, et al. Severity of lung involvement on chest X-rays in SARS-coronavirus-2 infected patients as a possible tool to predict clinical progression: an observational retrospective analysis of the relationship between radiological, clinical, and laboratory data. J Bras Pneumol. 2020;46(5):e20200226. https://doi.org/10.36416/1806-3756/e20200226
16. Chate RC, Fonseca EKUN, Passos RBD, Teles GBDS, Shoji H, Szarf G. Presentation of pulmonary infection on CT in COVID-19: initial experience in Brazil. J Bras Pneumol. 2020;46(2):e20200121. https://doi.org/10.36416/1806-3756/e20200121

Heterogeneity in rheumatoid arthritis-associated interstitial lung disease: time for splitting?

Leticia Kawano-Dourado[1,2,3], Karina Bonfiglioli[4]

Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is the second leading cause of death in patients with RA, with a 5-year mortality rate of 35%.[1] The prevalence of RA-ILD varies widely (from 1% to 30%) depending on the characteristics of RA patients and on how RA is defined.[1,2] RA-ILD has a spectrum of manifestations, ranging from inflammation (acute diffuse alveolar damage, organizing pneumonia, or nonspecific interstitial pneumonia) to fibrosis, manifested most commonly as usual interstitial pneumonia (UIP). Interestingly, accumulated evidence suggests that RA-UIP distinguishes a subpopulation of RA patients in whom risk factors, prognosis, and possibly treatment response might be different from those in patients with non-UIP RA-ILD.

RA-UIP is associated with the rs35705950 polymorphism in the promoter of the *MUC5B* gene, the same (and greatest) genetic risk factor for idiopathic pulmonary fibrosis, whereas non-UIP RA-ILD is not.[3] The molecular profile associated with RA-UIP is also different from that associated with non-UIP RA-ILD, meaning different protein expression most likely due to different pathogenic pathways.[4] Similarly, articular disease activity has been associated with the incidence of non-UIP RA-ILD; however, it remains unknown whether articular disease activity is associated with RA-UIP.[5]

Studies of RA-ILD differ from one another with regard to the proportion of RA-UIP patients in comparison with that of non-UIP RA-ILD patients. This might explain, at least in part, the divergent findings across studies.

In this issue of the JBP, Rosseti-Severo et al. report on the risk factors associated with RA-ILD in a single-center study.[6] Of 134 RA patients undergoing chest HRCT and pulmonary function testing, 36% had RA-ILD, which was associated with being > 62 years of age and having moderate to high articular disease activity.[6] RA-ILD was not stratified as being either RA-UIP or non-UIP RA-ILD.[6] Interestingly, the findings of Rosseti-Severo et al.[6] are consistent with those of previous studies.[5,7] For instance, in a study by Sparks et al., females constituted more than 80% of the study population, and nonspecific interstitial pneumonia accounted for more than 80% of the RA-ILD subphenotype.[8] In the study by Rosseti-Severo et al., females constituted 89% of the study population.[6] Therefore, we can speculate that most of the patients had non-UIP RA-ILD.

It is of note that the control group in the study by Rosseti-Severo et al.[6] consisted of RA patients without ILD, meaning that the control group probably included patients with RA-associated airway disease. This might explain why risk factors such as cigarette smoking and the presence of disease antibodies were not associated with RA-ILD in their study.[6]

The accumulated evidence so far suggests that RA-UIP is significantly different from non-UIP RA-ILD. Therefore, risk factors for incident disease, as well as disease progression and response to treatment, should be investigated with that in mind. The systematic reporting of the proportion of RA-UIP patients in studies of RA-ILD is a great start. However, our minds should remain open to the fact that this splitting (subphenotyping) might not yet be telling the whole story of RA-ILD.

"*You only find what you are looking for*."
Mary Leakey

REFERENCES

1. Raimundo K, Solomon JJ, Olson AL, Kong AM, Cole AL, Fischer A, et al. Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality [published correction appears in J Rheumatol. 2019 Feb;46(2):218]. J Rheumatol. 2019;46(4):360-369. https://doi.org/10.3899/jrheum.171315
2. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76(10):1700-1706. https://doi.org/10.1136/annrheumdis-2017-211138
3. Juge PA, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. N Engl J Med. 2018;379(23):2209-2219. https://doi.org/10.1056/NEJMoa1801562
4. Kass DJ, Nouraie M, Glassberg MK, Ramreddy N, Fernandez K, Harlow L, et al. Comparative Profiling of Serum Protein Biomarkers in Rheumatoid Arthritis-Associated Interstitial Lung Disease and Idiopathic Pulmonary Fibrosis [published correction appears in Arthritis Rheumatol. 2020 Apr;72(4):597]. Arthritis Rheumatol. 2020;72(3):409-419. https://doi.org/10.1002/art.41123
5. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid Arthritis Disease Activity Predicting Incident Clinically Apparent Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Prospective Cohort Study. Arthritis Rheumatol. 2019;71(9):1472-1482.

HCOR Research Institute, Hospital do Coração, São Paulo (SP) Brasil.
Divisão de Pneumologia, Instituto do Coração – InCor – Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
MAGIC Evidence Ecosystem Foundation, Oslo, Norway.
Divisão de Reumatologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

https://doi.org/10.1002/art.40904

6. Rosseti-Severo C, Chomiski C, Borba do Valle M, Escuissato D, Paiva E, Storrer K. Assessment of risk factors in patients with rheumatoid arthritis-associated interstitial lung disease. J Bras Pneumol. 2022;48(6):e20220145.
7. Restrepo JF, del Rincón I, Battafarano DF, Haas RW, Doria M, Escalante A. Clinical and laboratory factors associated with interstitial lung disease in rheumatoid arthritis. Clin Rheumatol. 2015;34(9):1529-1536. https://doi.org/10.1007/s10067-015-3025-8
8. Esposito AJ, Sparks JA, Gill RR, Hatabu H, Schmidlin EJ, Hota PV, et al. Screening for preclinical parenchymal lung disease in rheumatoid arthritis. Rheumatology (Oxford). 2022;61(8):3234-3245. https://doi.org/10.1093/rheumatology/keab891

J Bras Pneumol. 2022;48(6):e20220441
https://dx.doi.org/10.36416/1806-3756/e20220441

Obesity and asthma: the egg, the chicken, or both?

Kozeta Miliku[1,2], Theo J Moraes[3], Padmaja Subbarao[2,3,4]

The simultaneous rise in the epidemics of childhood asthma and obesity leading to a combined phenotype[1,2] has driven research trying to answer which comes first: obesity or asthma. Asthma is a chronic inflammatory disease of the airways that is characterized by episodes of wheezing, shortness of breath, and chest tightness, whereas obesity, also an inflammatory disease, is characterized by excess body fat. In part due to the complexity of these conditions, accurately predicting which comes first, or if the two conditions co-develop remains challenging. Ideally, to help defining the egg or the chicken, detailed assessments of obesity (e.g., measures that reflect growth, or fat composition and distribution) and asthma phenotypes (including longitudinal data from birth cohort studies) are posited to be useful.

Thus far, several studies have tried to solve the puzzle.[3-5] However, much of this work has been observational and cross-sectional in design. In addition, the definition of obesity and asthma is not consistent between studies, making it difficult to compare results and derive strong conclusions. In the existing literature, BMI, skin fold thickness, weight-for-age, and body fat percentage are often used as obesity markers. Yet, these markers, despite being similar on the surface, may represent different underlying physiological and metabolic processes. For example, weight-for-age may reflect a growth metric (e.g., birth weight may be used as a marker of intrauterine growth). Conversely, body fat percentage may be a measure of obesity or could represent an inflammatory trigger marker. Furthermore, it is recognized that differences in regional adiposity (e.g., visceral adiposity or skeletal mass) may have more relevance for asthma when compared to total body adiposity measures.[6] Similar issues exist for the definition of asthma. Although it is clear that there are different asthma endotypes, asthma is defined inconsistently throughout studies. The majority of studies define asthma based on the presence of wheezing in the last 12 months, and some require the presence of atopy or the support of lung function tests, or use a physician-diagnosis. The above heterogeneity makes it difficult to generate a clear understanding of the relationship between asthma and obesity.

To add to the complexity of the definitions, study designs, populations, and data analyses are also factors that often contribute to the inconsistent findings. While we know that there are sex[7-9] and ethnic[10] differences in asthma and obesity prevalence during different stages of development (e.g., puberty), sex- and age-stratified analyses are often neglected. Despite the heterogeneity in designs, populations, and analysis strategies, the data do suggest an association between asthma and obesity, two leading causes of chronic disease.

In this issue of the *Brazilian Journal of Pulmonology,* Weisshahn et al.[11] presented data from the longitudinal 1993 birth cohort in the city of Pelotas, Brazil. The authors explored obesity (defined by BMI cut-offs) and asthma (defined as wheezing in the last 12 months). They used bidirectional analyses with exposures collected at ages 11, 15, and 18 years, and outcomes measured at the age of 22 years. Overall, a bidirectional association was seen between obesity and asthma, with greater odds in the asthma-to-obesity direction, especially in females. The authors accounted for several covariates in their analyses (including parental history of asthma, birth weight, gestational age at birth, smoking, physical activity, use of corticosteroids, etc.) and speculate potential mechanisms to explain their findings. The authors also discussed similar analyses published before from their cohort at a younger age and revealed that obese adolescents have higher odds of wheezing. While the results from Weisshahn et al.[11] are very intriguing and add to the existing body of literature, future work will refine these observations.

Specifically, studies examining the obesity-asthma association would benefit from: a) longitudinal data collected from birth onwards; b) detailed phenotypes; c) an examination early in life for combined syndromes; d) samples defining inflammatory profiles/signatures; e) the use of artificial intelligence and machine learning approaches to define trajectories that lead to both asthma/wheezing and obesity. The future looks promising as longitudinal birth cohort studies offer datasets that will advance the understanding of early life trajectories and the evolution of asthma and obesity.[12,13]

While there are speculated and unanswered mechanisms about how obesity and asthma are linked, our CHILD Cohort Study[14] data suggest that traits of wheezing may be reflected by smaller lungs in part as a consequence of extra weight on airways,[15] which in addition might be triggered by or a trigger for inflammation. This last piece is supposition and needs a deeper look into acute or accumulated inflammatory markers (e.g., CRP and GlycA). It will be of interest to understand if acute inflammation can trigger asthma and obesity simultaneously, or if accumulation of inflammation triggers one of them first. Employing a life course approach to identify critical risk factors and pathways that alter an individual's physiology

1. Department of Nutritional Sciences, University of Toronto, Toronto (ON) Canada.
2. Department of Medicine, McMaster University, Hamilton (ON) Canada.
3. Program in Translational Medicine, Hospital for Sick Children, University of Toronto, Toronto (ON) Canada.
4. Department of Physiology, University of Toronto, Toronto (ON) Canada.

to increase the risks of asthma and obesity will ultimately translate into the development of early life interventions to promote lifelong health. So, which comes first, obesity or asthma? For now, we can say both.

REFERENCES

1. Reyes-Angel J, Kaviany P, Rastogi D, Forno E. Obesity-related asthma in children and adolescents. Lancet Child Adolesc Health. 2022;6(10):713-724. https://doi.org/10.1016/S2352-4642(22)00185-7
2. Redd SC, Mokdad AH. Invited commentary: obesity and asthma--new perspectives, research needs, and implications for control programs. Am J Epidemiol. 2002;155(3):198-202. https://doi.org/10.1093/aje/155.3.198
3. Chen Z, Salam MT, Alderete TL, Habre R, Bastain TM, Berhane K, et al. Effects of Childhood Asthma on the Development of Obesity among School-aged Children. Am J Respir Crit Care Med. 2017;195(9):1181-1188. https://doi.org/10.1164/rccm.201608-1691OC
4. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. Am J Epidemiol. 2003;158(5):406-415. https://doi.org/10.1093/aje/kwg175
5. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. Thorax. 2001;56(11):835-838. https://doi.org/10.1136/thorax.56.11.835
6. Mensink-Bout SM, Santos S, van Meel ER, Oei EHG, de Jongste JC, Jaddoe VWV, et al. General and Organ Fat Assessed by Magnetic Resonance Imaging and Respiratory Outcomes in Childhood. Am J Respir Crit Care Med. 2020;201(3):348-355. https://doi.org/10.1164/rccm.201905-0942OC
7. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. Am J Epidemiol. 2002;155(3):191-197. https://doi.org/10.1093/aje/155.3.191
8. Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. Arch Intern Med. 1999;159(21):2582-2588. https://doi.org/10.1001/archinte.159.21.2582
9. Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. Clin Exp Allergy. 1999;29(3):323-329. https://doi.org/10.1046/j.1365-2222.1999.00455.x
10. Moraes TJ, Sears MR, Subbarao P. Epidemiology of Asthma and Influence of Ethnicity. Semin Respir Crit Care Med. 2018;39(1):3-11. https://doi.org/10.1055/s-0037-1618568
11. Weisshahn NK, Oliveira PD, Wehrmeister FC, Gonçalves H, Menezes AMB. The bidirectional association between wheezing and obesity during adolescence and the beginning of adulthood in the 1993 birth cohort, Pelotas, Brazil. J Bras Pneumol.2022;48(6):e20220222.
12. Dai R, Miliku K, Gaddipati S, Choi J, Ambalavanan A, Tran MM, et al. Wheeze trajectories: Determinants and outcomes in the CHILD Cohort Study. J Allergy Clin Immunol. 2022;149(6):2153-2165. https://doi.org/10.1016/j.jaci.2021.10.039
13. Reyna ME, Petersen C, Dai DLY, Dai R, Becker AB, Azad MB, et al. Longitudinal body mass index trajectories at preschool age: children with rapid growth have differential composition of the gut microbiota in the first year of life. Int J Obes (Lond). 2022;46(7):1351-1358. https://doi.org/10.1038/s41366-022-01117-z
14. Subbarao P, Anand SS, Becker AB, Befus AD, Brauer M, Brook JR, et al. The Canadian Healthy Infant Longitudinal Development (CHILD) Study: examining developmental origins of allergy and asthma. Thorax. 2015;70(10):998-1000. https://doi.org/10.1136/thoraxjnl-2015-207246
15. Miliku K, Reyna M, Rastogi D, Dai R, Becker A, Turvey SE, et al. Associations of Somatic Growth Patterns and Asthma Development: The CHILD Cohort Study. DOHaD WORLD CONGRESS 2022; 2022 Aug 27-31; Vancouver, Canada; 2022.

J Bras Pneumol. 2022;48(6):e20220445
https://dx.doi.org/10.36416/1806-3756/e20220445

Is cystic fibrosis a risk factor for COVID-19 infection or related complications?

Rodrigo A Athanazio[1]

Since the beginning of the COVID-19 pandemic, pulmonologists all around the world have had to deal with several new challenges and uncertainties. As if the need to understand a new disease and how to manage it was not enough, another major challenge was to assess the impact of COVID-19 on people with respiratory diseases. Rapidly, the presence of respiratory comorbidities has emerged as an independent risk factor for complications related to SARS-CoV-2 infection.[1] However, has every patient with a chronic respiratory disease been at an increased risk of infection and unfavorable evolution related to the new coronavirus?

The cystic fibrosis (CF) community raised great concern about the impact of COVID-19 in CF patients since other viral infections had already been associated to worse outcomes and a considerable number of CF patients have impaired lung function.[2] With the social distancing measures suggested to control the pandemic, most CF patients adopted strict preventive measures that included the use of masks and lockdown. These measures, highly recommended and beneficial for patients, made it difficult to assess the real impact of SARS-CoV-2 infection on CF population.

In this issue of the *Jornal Brasileiro de Pneumologia*, Camargo et al.[3] described clinical characteristics and outcomes of incident cases of COVID-19 in unvaccinated adult CF individuals during the first year of pandemic. The cumulative incidence rate in the CF cohort was similar to that observed for the general population when adjusted for age. Also, severity of disease seemed not to be negatively influenced by the presence of CF. Almost the entire sample recovered completely from the infection, with few patients needing hospitalization, and only one death occurred in a patient with advanced lung disease (FEV_1 < 30% of the predicted value).

The first large description involving 181 CF patients diagnosed with COVID-19 described similar findings.[4] In that study, infection with SARS-CoV-2 exhibited a similar spectrum of outcomes to that seen in the general population. A more severe clinical course was associated with older age, CF-related diabetes, and poorer lung function in the year prior to infection, as well as in cases of organ transplant recipients.[4] Camargo et al.[3] highlighted the absence of transplanted or immunosuppressed patients, which may have reduced the possibility of unfavorable events related to SARS-CoV-2 infection. A more recent and larger publication with 1,452 cases of CF patients infected with SARS-CoV-2 confirmed that most CF patients have mild symptoms and good recovery after the infection.[5] However, comorbidities such as CF-related diabetes, impaired lung function, and immunosuppression once again have proven to be risk factors for severe complications.[5] Several reports and case series have confirmed the association of lung transplantation in patients with CF and severe forms of COVID-19.[6-8] These data reinforce that transplant-related immunosuppression would be a contributing factor to a greater risk of complications than CF itself. However, we are far from assuming that there are no COVID-19-related risks for CF patients. It is important to be aware of the constant and rapid changes related to the pandemic. The initiation of vaccination undoubtedly reduced the number of complications and severity of conditions associated with SARS-CoV-2 infection. Nevertheless, the emergence of new variants requires constant monitoring of potential new complications.[9]

Even experiencing a harrowing scenario such as the COVID-19 pandemic, it is necessary to seek for positive learnings during the process. The need for social distancing has allowed the development of numerous tools and strategies for the follow-up of patients with CF by using telemedicine and telemonitoring.[10] In addition, greater adherence to treatment, use of masks, and social distancing were associated with a significant reduction in the number of exacerbations.[11] These learnings must be incorporated into the new scenario of CF management in order to maintain better quality of life as well as preservation of lung function.

The COVID-19 pandemic is far from over. New variants have triggered new waves of infection across the world. Despite the positive results presented by most of the CF population infected with SARS-CoV2 so far, we must maintain preventive care and implement the acquired lessons. It is important to emphasize the relevance of vaccination, adherence to treatment, and use of masks, especially in hospital environments. The use of masks, in addition to protecting against viral infections, is an important measure to avoid cross-contamination by bacteria in the airways of these individuals. CF patients appear not to be at an increased risk of infection or developing complications related to COVID-19 when compared with the general population. However, this does not mean that there are no risks. As the pandemic evolves, new discoveries are emerging, as are new challenges. Given this, we must remember an important motto: "prevention is always the best medicine."

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

REFERENCES

1. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2020;383(25):2451-2460. https://doi.org/10.1056/NEJMcp2009575
2. Wat D, Doull I. Respiratory virus infections in cystic fibrosis. Paediatr Respir Rev. 2003;4(3):172-177. https://doi.org/10.1016/S1526-0542(03)00059-9
3. Camargo CC, Jacobsen LB, Wilsmann J, Silveira MN, Rossi EP, Oliveira CT, et al. Clinical characteristics and outcomes of incident cases of COVID-19 in unvaccinated adult cystic fibrosis patients in southern Brazil: a prospective cohort study conducted during the first year of the COVID-19 pandemic. J Bras Pneumol. 2022;48(6):e20220265. https://doi.org/10.36416/1806-3756/e20220265
4. McClenaghan E, Cosgriff R, Brownlee K, Ahern S, Burgel PR, Byrnes CA, et al. The global impact of SARS-CoV-2 in 181 people with cystic fibrosis. J Cyst Fibros. 2020;19(6):868-871. https://doi.org/10.1016/j.jcf.2020.10.003
5. Carr SB, McClenaghan E, Elbert A, Faro A, Cosgriff R, Abdrakhmanov O, et al. Factors associated with clinical progression to severe COVID-19 in people with cystic fibrosis: A global observational study. J Cyst Fibros. 2022;21(4):e221-e231. https://doi.org/10.2139/ssrn.3990936
6. Myers CN, Scott JH, Criner GJ, Cordova FC, Mamary AJ, Marchetti N, et al. COVID-19 in lung transplant recipients. Transpl Infect Dis. 2020;22(6):e13364. https://doi.org/10.1111/tid.13364
7. Messika J, Eloy P, Roux A, Hirschi S, Nieves A, Le Pavec J, et al. COVID-19 in Lung Transplant Recipients. Transplantation. 2021;105(1):177-186. https://doi.org/10.1097/TP.0000000000003508
8. Athanazio RA, Costa AN, Carraro RM, Gonzalez D, Rached SZ, Samano MN, et al. Early COVID-19 infection after lung transplantation in a patient with cystic fibrosis. Clinics (Sao Paulo). 2020;75:e2274. https://doi.org/10.6061/clinics/2020/e2274
9. Hadj Hassine I. Covid-19 vaccines and variants of concern: A review. Rev Med Virol. 2022;32(4):e2313. https://doi.org/10.1002/rmv.2313
10. Rad EJ, Mirza AA, Chhatwani L, Purington N, Mohabir PK. Cystic fibrosis telemedicine in the era of COVID-19. JAMIA Open. 2022;5(1):ooac005. https://doi.org/10.1093/jamiaopen/ooac005
11. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Patel S, Thompson MD, Slaven JE, Sanders DB, Ren CL. Reduction of pulmonary exacerbations in young children with cystic fibrosis during the COVID-19 pandemic. Pediatr Pulmonol. 2021;56(5):1271-1273. https://doi.org/10.1002/ppul.25250

Dense reticular pattern

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

A 23-year-old woman with no respiratory symptoms and a previous diagnosis of lupus nephritis underwent chest CT examination, which showed reticular opacities in the lower lung lobes, arranged in a branching network pattern (Figure 1). On physical examination, she was breathing normally. Cardiopulmonary auscultation was unremarkable, as were laboratory test results. A diagnosis of dendriform pulmonary ossification was made on the basis of the chest CT findings.

Diffuse pulmonary ossification is a rare chronic condition characterized by mature bone formation in the lung parenchyma. Diffuse pulmonary ossification can be idiopathic or associated with a variety of pulmonary, cardiac, and systemic disorders. It is classified as nodular or dendriform, with the former usually occurring in the context of chronic congestion. Diffuse pulmonary ossification is an interstitial process that occurs in a setting of fibrosing interstitial lung disease. It can progress to osseous metaplasia, which is seen in imaging studies as calcified nodular densities in a branching pattern. This pattern has been observed mainly in areas of reticulation rather than in areas of honeycombing.

Dendriform pulmonary ossification is characterized by interstitial branching spicules that contain occasional bone marrow islets with osteoblastic and osteoclastic activity. These spicules form a contiguous and branching pattern resembling tree branches. In most instances, they are of high attenuation, reflecting the underlying ossification. Dendriform pulmonary ossification usually goes undetected on chest X-rays, being typically diagnosed postmortem. A chest CT scan with appropriate window settings can show tiny calcified opacities in the lung periphery. The detection of small high-attenuation foci is improved by thin-slice acquisition and maximum intensity projection imaging.[1-3]

A dendriform pulmonary ossification pattern can be detected by imaging in patients who are asymptomatic or who have mild symptoms. It has also been described in association with recurrent aspiration, and as a cause of pneumothorax.[1-3] Dendriform pulmonary ossification has recently been related to cicatricial organizing pneumonia.[3] This distinctive form of organizing pneumonia can manifest as persistent linear opacities that mimic fibrosing interstitial pneumonia. It can also appear as foci of ossification in imaging and pathological studies, and has been reported in patients with COVID-19 pneumonia.[2]

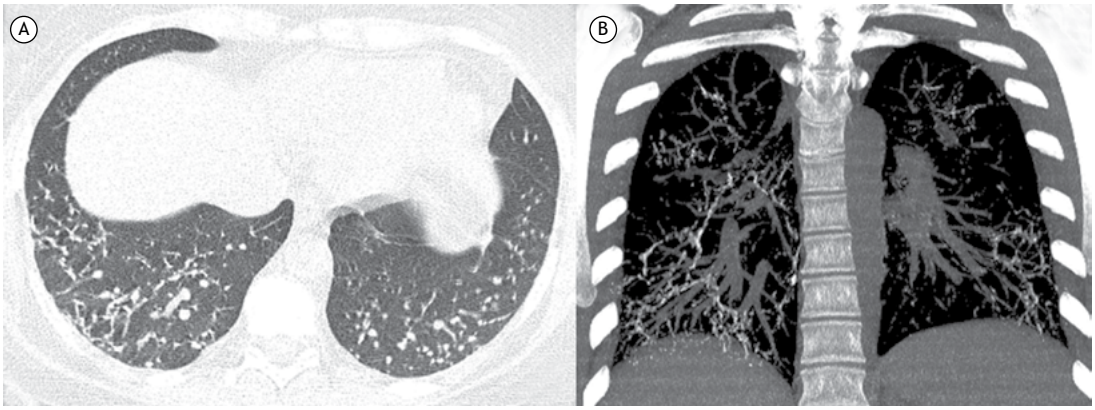

Figure 1. In A, unenhanced axial chest CT scan with lung window settings, showing reticular opacities in the lower lobes of the lungs. In B, coronal reconstruction with bone window settings and maximum intensity projection, showing interstitial calcifications arranged in a branching network pattern.

REFERENCES

1. Marchiori E, Souza AS Jr, Franquet T, Müller NL. Diffuse high-attenuation pulmonary abnormalities: a pattern-oriented diagnostic approach on high-resolution CT. AJR Am J Roentgenol. 2005;184(1):273-282. https://doi.org/10.2214/ajr.184.1.01840273
2. Torres PPTES, Rabahi MF, Marchiori E. Dendriform pulmonary ossification in coronavirus disease 2019 pneumonia. Rev Soc Bras Med Trop. 2022;55:e0621. https://doi.org/10.1590/0037-8682-0621-2021
3. Bin Saeedan M, Farver C, Mehta AC, Yadav R. Cicatricial Organizing Pneumonia with Dendriform Pulmonary Ossification: An Unusual Cause for a Recurrent Pneumothorax. Case Rep Pulmonol. 2019;2019:2379145. https://doi.org/10.1155/2019/2379145

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

Linear and logistic regression models: when to use and how to interpret them?

Horacio Matias Castro[1,2], Juliana Carvalho Ferreira[1,3]

PRACTICAL SCENARIO

A secondary analysis[1] of a study designated "Integrating Palliative and Critical Care," a cluster randomized trial, was conducted to explore differences in receipt of elements of palliative care among patients who died in the ICU with interstitial lung disease (ILD) or COPD in comparison with those who died of cancer. The authors used two methods of multiple regression analysis: linear regression to estimate the impact of COPD and ILD, in comparison with that of cancer, on the length of ICU stay, and logistic regression to evaluate the effects of COPD and ILD on the presence or absence of elements of palliative care. All regression models were adjusted for confounders (age, sex, minority status, education level, among others) of the association between the patient diagnosis and palliative care outcomes.

INTRODUCTION

Linear and logistic regressions are widely used statistical methods to assess the association between variables in medical research. These methods estimate if there is an association between the independent variable (also called predictor, exposure, or risk factor) and the dependent variable (outcome).[2]

The association between two variables is evaluated with simple regression analysis. However, in many clinical scenarios, more than one independent variable may be associated with the outcome, and there may be the need to control for confounder variables. When more than two independent variables are associated with the outcome, multiple regression analysis is used. Multiple regression analysis evaluates the independent effect of each variable on the outcome, adjusting for the effect of the other variables included in the same regression model.

WHEN TO USE LINEAR OR LOGISTIC REGRESSION?

The determinant of the type of regression analysis to be used is the nature of the outcome variable. Linear regression is used for continuous outcome variables (e.g., days of hospitalization or FEV1), and logistic regression is used for categorical outcome variables, such as death. Independent variables can be continuous, categorical, or a mix of both.

In our example, the authors wanted to know if there was a relationship between cancer, COPD, and ILD (baseline disease; the independent variables) with two different outcomes. One outcome was continuous (length of ICU stay) and the other one was categorical (presence or absence of elements of palliative care). Therefore, two models were built: a linear model to examine the association between baseline disease (chronic pulmonary disease or cancer) and length of ICU stay, and a logistic regression analysis to examine the association between the baseline disease and being in receipt of elements of palliative care.

HOW TO INTERPRET RESULTS OF REGRESSION ANALYSIS?

Regression models are performed within statistical packages, and the output results include several parameters, which can be complex to interpret. Clinicians who are learning the basics of regression models should focus on the key parameters presented in Chart 1.

In our example, the baseline disease—COPD, ILD, or cancer (the reference category)—is the independent variable, and length of ICU stay and receipt of palliative care elements are the outcomes of interest. In addition, the regression models also included other independent variables considered as potential confounders, such as age, sex, and minority status. In the linear regression model, the length of ICU stay for patients with ILD was longer than for those with cancer ($\beta = 2.75$; 95% CI, 0.52-4.98; $p = 0.016$), which means that, on average, having ILD increased the length of ICU stay in 2.75 days when compared with the length of ICU stay among cancer patients. In the logistic regression model, the authors found that patients with ILD, when compared with cancer patients, were less likely to have any documentation of their pain assessment in the last 24 h of life (OR = 0.43; 95% CI, 0.19-0.97; $p = 0.042$), which means that having ILD decreased the odds of documentation of pain assessment by more than half.

KEY POINTS

- Linear and logistic regressions are important statistical methods for testing relationships between variables and quantifying the direction and strenght of the association.
- Linear regression is used with continuous outcomes, and logistic regression is used with categorical outcomes.
- These procedures require expertise in regression model building and typically require the assistance of a biostatistician.

1. Methods in Epidemiologic, Clinical, and Operations Research-MECOR-program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. Pulmonary Medicine Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
3. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ISSN 1806-3756

Chart 1. Most important parameters in regression analyses and their interpretations.

Parameter	Linear regression	Logistic regression
Direction and strength of the association between the independent variable and the dependent variable (outcome)	Beta coefficient: Describes the (expected) average change in the outcome variable for each one-unit change in the independent variable for continuous variables, or the average change in the outcome variable for one category of the independent variable compared with a reference category for categorical variables	OR: The OR for a continuous independent variable is interpreted as the change in the odds of the outcome occurring for every one-unit increase in the independent variable The OR for categorical independent variables is interpreted as the increase or decrease in odds between two categories (e.g., men vs women) OR = 1: no association; OR > 1: positive association or risk factor; and OR < 1: negative association or protective factor
Example (for a continuous independent variable)	The expected increase in FEV_1 for each centimeter increase in height	The expected increase in the odds of death for each increase of one year of age among patients with sepsis
Example (for a categorical independent variable)	The expected increase in FEV_1 for men compared with women with the same height and age	The expected increase in the odds of death for men compared with women among COVID-19 patients
Precision of the estimate	The 95% CI of the beta coefficient	The 95%CI of the OR
Statistical significance	The p value (significant when < 0.05)	The p value (significant when < 0.05)

REFERENCES

1. Brown CE, Engelberg RA, Nielsen EL, Curtis JR. Palliative Care for Patients Dying in the Intensive Care Unit with Chronic Lung Disease Compared with Metastatic Cancer. Ann Am Thorac Soc. 2016;13(5):684-689. https://doi.org/10.1513/AnnalsATS.201510-667OC
2. Bzovsky S, Phillips MR, Guymer RH, Wykoff CC, Thabane L, Bhandari M, et al. The clinician's guide to interpreting a regression analysis. Eye (Lond). 2022;36(9):1715-1717. https://doi.org/10.1038/s41433-022-01949-z

Small airway disease: when the "silent zone" speaks up

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

BACKGROUND

The human airways consist of approximately 23 generations of dichotomously branching tubes from the trachea to the alveoli. From generation 8 downstream, the small airways (< 2 mm in diameter) lack cartilaginous support, being more easily compressible/collapsible. Given the exponential increase in airway numbers, there is a rapid increase in total cross-sectional area; thus, airflow velocity decreases, and small airways resistance comprises only 10-20% of total airways resistance. It follows that extensive functional abnormalities in the so-called "silent zone" might not be detected by routine pulmonary function tests.[1]

OVERVIEW

A 68-year-old nonsmoker male (BMI = 41.2 kg/m^2) was referred for respiratory assessment due to insidious exertional dyspnea and dry cough. He had undergone hematopoietic stem cell transplantation approximately one year prior in the setting of acute myeloblastic leukemia. There was no clinical or laboratory evidence of graft-versus-host disease. Spirometry revealed no obstruction, and $FEF_{25-75\%}$ was reduced in proportion to a low FVC. Plethysmography showed a trend toward low "static" lung volumes and high specific airway resistance. Taken together, these results were considered equivocal in a severely obese subject[2] with a history of right upper lobectomy for congenital disease. Given concerns of incipient bronchiolitis obliterans, he was referred for more sensitive tests of small airway disease (SAD), the results of which were as follows: increased phase III slope and closing capacity (single-breath N_2 washout), increased ventilation heterogeneity in acinar airways relative to conducting airways (multiple-breath N_2 washout), and increased difference between resistance at 5 Hz and 20 Hz (impulse oscillometry). As it can be seen in Chart 1, these results were indeed consistent with SAD. Despite mild gas trapping without mosaic attenuation on chest CT, the consistency of the functional findings prompted immunosuppressive therapy. At the three-month follow-up visit, there was resolution of symptoms and uniform improvement in all functional markers of SAD.

Diagnosing SAD might be clinically relevant in the initial stages of several obstructive lung diseases, including asthma,[3] cystic fibrosis, and COPD. Tests of SAD may also reveal unsuspected airway abnormalities in sarcoidosis and some interstitial lung diseases, such as hypersensitivity pneumonitis and nonspecific interstitial pneumonia. Detecting SAD may change management in connective tissue diseases (e.g., rheumatoid arthritis, mixed disease), inflammatory bowel diseases, bone marrow and lung transplantation, common variable immunodeficiency disorders, diffuse panbronchiolitis, and diseases related to environmental exposures to pollutants, allergens, and drugs.[4] As herein described, insidious SAD might be a late complication of hematopoietic stem cell transplantation, even in the absence of graft-versus-host disease. Prompt aggressive treatment is paramount to improving survival.[5]

CLINICAL MESSAGE

Although physiological tests interrogating the "silent zone" are not widely available, they can provide valuable information in cases when the diagnosis and quantification of SAD might impact on clinical decision making. The lack of reliable reference values and cut-offs for abnormality remains an extant issue: in many circumstances, longitudinal worsening—or improvement in response to treatment—is more useful. If feasible, combining techniques (Chart 1) further improves diagnostic accuracy.

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

ISSN 1806-3756

Chart 1. Selected techniques aimed at diagnosing and quantifying the severity of small airway disease.

Technique fundamentals	Rationale for key variables	Caveats and limitations
Spirometry Abnormally slow airflow relative to forced expired volume signals airway obstruction. Air from larger proximal airways is expired earlier and at a greater speed, whereas air from smaller distal airways is expired later and at a slower speed.	• ⇩ **$FEF_{25-75\%}$** As lung volume falls, diseased small airways collapse at an earlier time and closer to the alveolus. This reduces the maximum expiratory flow that can be achieved during mid- to late expiration. • ⇩ **FEV_3/FVC and/or ⇧ 1 − (FEV_3/FVC)** By considering flows over a longer period, FEV_3 includes a larger fraction of small airways, estimating the growing proportion of units with longer time constants. • ⇩ **FEV_1/FEV_6 and/or ⇩ FEV_3/FEV_6** Using FEV_6 may reduce the impact of a variable FVC in these ratios. • ⇧ Slow VC (SVC)-FVC difference In the presence of SAD, more air is exhaled when there is less airway compression during the slow maneuver. This might lead to low FEV_1/SVC despite preserved FEV_1/FVC.	Bronchodilating effects of deep inspiration might increase FEVs, masking (mild) bronchoconstriction. $FEF_{25-75\%}$, in particular, is highly dependent on FVC: changes in FVC will markedly affect the portion of the flow-volume curve examined. None of these variables is specific to SAD; moreover, they are a) relatively insensitive to early disease, b) redundant to FEV_1/FVC in more advanced disease, and c) effort-dependent. There is a lack of reference values for FEV_1/SVC: this ratio declines with aging faster than does FEV_1/FVC, potentially over-diagnosing obstruction in the elderly.
Plethysmography ⇧ changes in box pressure relative to variations in mouth ("alveolar") pressure at end-tidal expiration signal ⇧ lung volume (FRC): RV is given by FRC − ERV. ⇧ changes in the pressure required to generate flow indicate ⇧ airway resistance at a given lung volume (sR_{aw}).	• ⇧ **RV and/or ⇧ RV/TLC** RV and RV/TLC are elevated in the presence of premature airway closure and air trapping. RV/TLC may be a more useful marker of gas trapping as TLC might be increased in obstructive lung disease. • ⇧ **sR_{aw} and/or ⇩ $1/sR_{aw}$ (sG_{aw})** sR_{aw} and sG_{aw} might be abnormal in the presence of widespread SAD. FEV_1 is sensitive to changes occurring upstream from the choke point, whereas sR_{aw} is sensitive to changes in resistance anywhere along the airway. sR_{aw} may change without significant change in FEV_1.	RV is not directly measured: errors in IC and/or SVC may lead to spuriously high RV. High RV/TLC in the presence of preserved TLC may be seen in patients with expiratory muscle weakness. sR_{aw} and sG_{aw} are very sensitive to central airway pathology but less sensitive to peripheral changes (unless there is widespread SAD). Both have wide limits of normal.
Single-breath N_2 washout After inhalation of 100% O_2, exhaled N_2 is measured from TLC to RV. In phase I, N_2 is not detected (Vd_{ana}). Subsequently, exhaled N_2 rises swiftly (phase II) followed by a slowly rising alveolar "plateau" (phase III). In phase IV, exhaled N_2 increases when better-ventilated units close and less-ventilated regions (less exposed to O_2; thus, richer in N_2) empty.	• ⇧ **phase III slope** A flat phase III slope indicates that all units received the same amount of O_2, emptying simultaneously. A steep phase III slope indicates the sequential emptying of units with different N_2 concentrations due to patchy disease. • ⇧ **volume above RV at which phase IV starts (closing capacity)** The higher the closing capacity as a fraction of VC, the earlier the closure of the gravity-dependent small airways. Thus, the higher the closing capacity, the greater the trend toward gas trapping.	The pleural pressure gradient may contribute to regional differences in N_2 concentration: regional differences in air-space compliance may create differences in the time required to fill and empty different lung regions. Changes in any of the generations of the conducting airways may affect the phase III slope. Closing capacity increases with increasing intraabdominal pressure, age, decreased pulmonary blood flow, and pulmonary parenchymal lung disease associated with poor compliance.
Multiple-breath N_2 washout After inhalation of 100% O_2, sequential single breaths are followed as N_2 is progressively washed out. Whereas the phase III slopes of the initial breaths are strongly influenced by S_{acin}, the progressive increase in slopes thereafter is thought to be influenced by S_{cond}.	• ⇧ **lung clearance index** The higher the lung turnovers (FRC equivalents) required to wash out the tracer gas (N_2) to $1/40^{th}$ of the original concentration, the lower the gas mixing efficiency across the whole lung, i.e., poor global ventilation homogeneity. • **S_{acin} and S_{cond}** ⇧ S_{acin} indicates ventilation inhomogeneity distal to the terminal bronchioles, i.e., in the small airways. As such, it is frequently seen in smokers with preserved FEV_1. Conversely, S_{cond} is more closely related to sG_{aw} and forced expiratory flows, i.e., larger airways function.	There are conflicting data on whether S_{cond} does provide a better metric of SAD compared with S_{acin} across different obstructive airway diseases; there are technical controversies over the best approach to measure the phase III slope across multiple breaths; and a variable effect of different tidal volumes. There is critical dependence on accurate time matching between the flow sensor and the gas analyzer.

Continue...▶

Chart 1. Selected techniques aimed at diagnosing and quantifying the severity of small airway disease. (Continued...)

Technique fundamentals	Rationale for key variables	Caveats and limitations
Impulse oscillometry Airflow oscillations are artificially generated by a loudspeaker at frequencies from 2 Hz to 30 Hz and superimposed on the natural flows at tidal volume. Resistance represents impedance to airflow changes. At high frequencies, the oscillations might be "blocked" at the level of narrowed larger airways. At lower frequencies, the oscillations can pass over the larger airways, reflecting the whole lung resistance. Reactance represents impedance to volume changes.	• ⇧ $R_5 - R_{20}$ Since R_5 reflects the resistance of the entire trachea-bronchial tree where R_{20} is primarily influenced by the large airways caliber, their difference is biased to reflect the functional properties of the small airways. • ⇩ X_5 Since the lungs' ability to store capacitive energy is primarily manifest in the small airways, low reactance at low frequencies signals SAD. • ⇧ AX AX is the integrated low frequency respiratory reactance magnitude between 5 Hz and the resonant frequency, i.e., when inflation pressure and elastic recoil cancel each other in the transition from passive distension to active stretching. AX is related to respiratory compliance and therefore to small airway patency. AX closely correlates with $R_5 - R_{20}$.	Results vary by manufacturer. Impulse oscillometry measurements are influenced by extrathoracic upper airway artifacts (swallowing, glottis closure). Elastance or capacitance refers to energy return properties of the lung, like electric circuits, not stiffness during inflation (more intuitive for clinicians). Therefore, the reactance at lower frequencies would change in the same direction in fibrosis, emphysema, or SAD, i.e., it would become even more negative. Hence, the direction of change in reactance does not differentiate between obstructive and restrictive diseases.

⇩: decreased; FEV_3: forced expiratory volume in three seconds; ⇧: increased; FEV_6: forced expiratory volume in six seconds; SAD: small airway disease; FRC: functional residual capacity; ERV: expiratory reserve volume; sR_{aw}: specific airway resistance; sG_{aw}: specific airway conductance; IC: inspiratory capacity; $V_{D_{ana}}$: anatomic dead space; S_{acin}: ventilation heterogeneity in acinar airways; S_{cond}: ventilation heterogeneity in conducting airways; R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; X_5: reactance at 5Hz; and AX: reactance area.

REFERENCES

1. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. J Clin Invest. 1969;48(6):1097-1106. https://doi.org/10.1172/JCI106066
2. Neder JA, Berton DC, O'Donnell DE. Obesity: how pulmonary function tests may let us down. J Bras Pneumol. 2020;46(3):e20200116. https://doi.org/10.36416/1806-3756/e20200116
3. Jackson N, Rafique J, Singh D. Identifying small airway dysfunction in asthma in clinical practice. J Bras Pneumol. 2020;46(2):e20200046. https://doi.org/10.36416/1806-3756/e20200046
4. Burgel PR, Bergeron A, de Blic J, Bonniaud P, Bourdin A, Chanez P, et al. Small airways diseases, excluding asthma and COPD: an overview. Eur Respir Rev. 2013;22(128):131-147. https://doi.org/10.1183/09059180.00001313
5. Busmail A, Penumetcha SS, Ahluwalia S, Irfan R, Khan SA, Rohit Reddy S, et al. A Systematic Review on Pulmonary Complications Secondary to Hematopoietic Stem Cell Transplantation. Cureus. 2022;14(5):e24807. https://doi.org/10.7759/cureus.24807

J Bras Pneumol. 2022;48(6):e20220222
https://dx.doi.org/10.36416/1806-3756/e20220222

The bidirectional association between wheezing and obesity during adolescence and the beginning of adulthood in the 1993 birth cohort, Pelotas, Brazil

Nícolas Kickhofel Weisshahn[1], Paula Duarte de Oliveira[1], Fernando César Wehrmeister[1], Helen Gonçalves[1], Ana Maria Baptista Menezes[1]

1. Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas (RS), Brasil.

Submitted: 14 June 2022
Accepted: 30 August 2022

Study carried out at the Centro de Pesquisas Epidemiológicas, Universidade Federal de Pelotas, Brazil.

ABSTRACT

Objective: To analyze the bidirectional association between wheezing and obesity during adolescence and the beginning of adulthood in a cohort in southern Brazil. **Methods:** This prospective longitudinal study used data from the 1993 birth cohort in Pelotas, Brazil. The following outcome variables were measured at 22 years of age: self-reported wheezing during the last 12 months and obesity (BMI ≥ 30 kg/m^2). The following exposure variables were measured at ages 11, 15, and 18: self-reported wheezing (no wheezing or symptom presentation in 1, 2, or 3 follow-ups) and obesity (non-obese or obese in 1, 2, or 3 follow-ups). Crude and adjusted logistical regression stratified by sex were used in the analyses. The reference category was defined as participants who presented no wheezing or obesity. **Results:** A total of 3,461 participants had data on wheezing and 3,383 on BMI. At 22 years of age, the prevalence of wheezing was 10.1% (95%CI: 9.1; 11.2), and obesity, 16.2% (95%CI: 15.0; 17.6). In females, the presence of wheezing in two follow-ups revealed a 2.22-fold (95%CI: 1.36; 3.61) greater chance of developing obesity at 22 years of age. Meanwhile, the presence of obesity in two follow-ups resulted in a 2.03-fold (95%IC: 1.05; 3.92) greater chance of wheezing at 22 years of age. No associations were found between wheezing and obesity in males. **Conclusions:** The obtained data suggest a possible positive bidirectional association between wheezing and obesity, with greater odds ratios in the wheezing to obesity direction in females and in the category of occurrence of exposure in two follow-ups.

Keywords: Asthma, BMI, Respiratory Sounds, Wheezing, Body Weight.

INTRODUCTION

In recent years, the literature has shown a positive association between wheezing and obesity.[1-3] Furthermore, the Global Initiative for Asthma (GINA) annually reiterates the importance of research in this field, given that asthmatic obese patients display worse disease control and a greater burden and frequency of symptoms, interfering with their quality of life.[4]

A systematic review proposed the possibility of obesity being a risk factor or effect modifier for wheezing status.[5] However, the literature is inconsistent in assuming a direction for the association or the possibility of common causes between asthma and obesity.[6,7] In order to clarify the relationship between these diseases and propose strategies for management and prevention, it is necessary to understand the contribution of each disease in the association in different populations with distinct socioeconomic and environmental aspects.[8,4]

The bidirectional analysis of the association between wheezing and obesity in longitudinal studies may be considered a recent approach in the literature. Some bidirectional longitudinal studies[9-11] indicated that obesity probably precedes the onset of asthma. Granell et al.[11] proposed that for each increment of 1 kg/m^2 in the Body Mass Index (BMI), the risk of developing asthma during infancy increases by 55%. In contrast, Zhang et al.[12] found that children diagnosed with asthma in any follow-up study had an approximately 40% greater chance of becoming obese in the subsequent follow-up. Therefore, the association directionality between these diseases remains uncertain.[6,7]

Thus, the aim of the present study was to explore the bidirectional association between wheezing and obesity in a cohort in southern Brazil, investigating the associations between a) the presence of wheezing during adolescence (11, 15, and 18 years of age) and the presence of obesity at age 22, and b) the presence of obesity during adolescence (11, 15, and 18 years of age) and the presence of wheezing at age 22.

METHODS

This was a longitudinal, prospective, and population-based study of the 1993 birth cohort in Pelotas, Brazil. In 1993, all live births whose families resided in the

Correspondence to:
Nícolas Kickhofel Weisshahn. Rua Marechal Deodoro, 1160, 3º andar, Pelotas (RS) – Brazil; CEP: 96020-220; Telefone/Fax: +55 (53) 3284 – 1300; Cell Phone: +55 (53) 98103 - 6733; E-mail: weisshahn.n@gmail.com.

urban area of Pelotas were eligible for the study and, subsequently, followed up at different ages for 22 years. The analyses included: a) participants who answered questions about wheezing in the follow-ups conducted at 11, 15, and 18 years of age and with anthropometric measurements at age 22, and b) participants with anthropometric measurements at 11, 15, and 18 years of age and with information on wheezing collected in the follow-up at age 22. More details concerning the cohort's methodology may be found in previous publications.[13-15]

In order to investigate the bidirectional association, the variables of interest herein were wheezing (chest wheezing) and BMI. The wheezing variable was defined according to the "International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee"[16] and measured using a questionnaire validated for the Brazilian population.[17] Treated as a binary variable, participants were considered to present wheezing after an affirmative response to the question related to the 12 months leading up to the follow-up visit: *"Since <month> of last year, have you experienced any chest wheezing?"*. The variable BMI (weight/height^2) was dichotomized using the cutoff points that characterize the presence of obesity. Participants who presented with a BMI ≥ + 2 z-scores at ages 11 and 15 and BMI ≥ 30.0 kg/m^2 at ages 18 and 22 were considered obese.[18] In the follow-ups at 11 and 15 years of age, the participants' weight was measured twice using a digital scale (Tanita, accuracy of 100 grams), while at ages 18 and 22, weight was obtained using the BOD POD® body composition tracking system (BOD POD® Composition System; COSMED, Albano Laziale, Italy). Height was measured with a stadiometer.

For the bidirectional analysis, the following combinations were used: a) presence of wheezing at ages 11, 15, and 18 as exposure and "obesity at 22 years of age" as the outcome, and b) obesity at ages 11, 15, and 18 as exposure and "wheezing at the 22-year follow-up" as the outcome. Exposure variables were generated for the presence of wheezing and obesity and were categorized as follows: absence of exposure in all three follow-ups, 1 follow-up (presence of exposure in one of the three follow-ups); 2 follow-ups (presence of exposure in two of the three follow-ups); always presenting exposure (presence of exposure in all three follow-up visits).

The covariates collected in the perinatal follow-ups were: sex (male/female), skin color (white/black/other), birthweight (grams), gestational age at birth (weeks), maternal schooling during pregnancy (years), maternal smoking during pregnancy (yes/no), family history (father and/or mother) of asthma (yes/no), and family income (minimum wages). At the 11-year follow-up, the covariates of interest were: family income (in Reais) and parental smoking (never/ex-smoker/smoker). In order to characterize the sample at the 22-year follow-up, the following covariates were evaluated: schooling (years), asset index (quintiles), smoking (never smoked/ex-smoker/smoker), total physical activity (leisure and commuting) ≥ 150 min/week (yes/no), and the use of corticosteroids in the last three months (yes/no).

The categorical variables were described as relative frequencies and the respective 95% confidence intervals (95%CI). According to the perinatal follow-up variables, Pearson's chi-square test was used to compare the original cohort sample and the samples included in the analyses. The prevalence of obesity and wheezing at 22 years of age was described according to the demographic, socioeconomic, behavioral, and health variables, and either Pearson's chi-square test or a Chi-square test for linear trends was used according to the independent variables.

In order to test the crude and adjusted association between the outcomes wheezing and obesity at 22 years of age according to exposure (obesity and wheezing from ages 11 to 18, respectively), logistical regressions stratified by sex were used, regardless of the significance of the test of interaction. Confounders were determined *a priori* and included simultaneously in the analytical models. The confounding variables were defined as: skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, and family income and parental smoking at the 11-year follow-up. The p-value of the association analyses was given by the Wald Test. A 5% significance level was adopted, and the analyses were performed using the Stata 16.0 software (Stata Corp. LP, College Station, TX, USA).

The 1993 cohort follow-ups were approved by the Ethics Committee of the Federal University of Pelotas, with the most recent protocol being No. 1.250.366, at 22 years of age. All participants or guardians were informed regarding the objectives of the study and signed a term of free and informed consent prior to the beginning of data collection, in accordance with the Declaration of Helsinki.

RESULTS

The 1993 cohort consisted of 5,249 live births, with follow-up rates of 87.5%, 85.7%, 81.4%, and 76.3% at ages 11, 15, 18, and 22, respectively. The present study's sample included 3,461 participants with complete wheezing information from 11 to 18 years of age, and 3,383 participants with BMI data from 11 to 18 years of age. No differences were observed in the distribution of perinatal characteristics between the original cohort sample and the samples included in the analyses (Table 1).

The prevalence of obesity and wheezing over the last 12 months at the 22-year follow-up according to demographic, socioeconomic, behavioral, and health variables is shown in Table 2. The prevalence of obesity was 16.2% (95%CI: 15.0; 17.6). The highest prevalence of obesity with statistical significance was observed in female participants as opposed to males (18.5% versus 13.7%), black skin color (19.1% versus

15.1% with white skin color), family history of asthma (18.6% versus 15.1% without a family history), and participants whose parents were ex-smokers at the 11-year follow-up (17.9% compared to 13.5% in those whose parents were non-smokers). The prevalence of obesity was 17.9% in the poorest asset index quintile at 22 years of age, whereas, in the wealthiest quintile, it was 10.8%. Also, participants with 12 or more years of schooling showed a lower prevalence of obesity (12.1%) when compared to the other categories.

The prevalence of wheezing in the last 12 months was 10.1% (95%CI: 9.1; 11.2). The highest prevalence of wheezing, with statistical significance, was observed in participants whose mothers had the least schooling (11.9% versus 8.9% of mothers with more years of schooling), smoked during pregnancy (12.1% versus 9.2% in non-smokers), and in participants with a parental history of asthma (14.7% versus 7.8% without parental history of asthma). Regarding the variables pertaining to the participants themselves, a larger prevalence of wheezing at the 22-year follow-up was found in those with fewer years of schooling (18.3% versus 8% with more years of schooling), in the poorest quintile compared to the richest (12.9% versus 7.7%), among smokers (20.1% versus 7.7% in non-smokers), among the obese (14% versus 9.5% in the non-obese), and among those who reported using corticosteroids in the last three months compared to those who did not use such medications (19.3% versus 8.5%) (Table 2).

During the period from 11 to 18 years of age, three follow-ups were carried out in the 1993 birth cohort. While the overall prevalence of wheezing in at least one of the follow-up visits was 23.2% (95%CI: 21.8; 24.6), 2.4% (95%CI: 1.9; 2.9) always reported the presence of the symptom. As for obesity, the overall prevalence in at least one follow-up was 11.4% (95%CI: 10.3; 12.5), and 3.7% (95%CI: 3.2; 4.4) were obese in all follow-ups. In the stratification by sex,

Table 1. Baseline characteristics of the original cohort and the samples included in the analyses. The 1993 Birth Cohort, Pelotas, Brazil.

		Included in the analyses[a]			
	Original Cohort (n = 5,249)	Wheezing from age 11 to 18 (n = 3,461)		Obesity from age 11 to 18 (n = 3,383)	
	% (95% CI)	% (95% CI)	p-value*	% (95% CI)	p-value*
Sex			0.098		0.249
Male	49.6 (48.2;51.0)	47.8 (46.1;49.5)		48.3 (46.6;50.0)	
Female	50.4 (49.0;51.7)	52.2 (50.5;53.9)		51.7 (50.0;53.3)	
Birthweight (grams)			0.521		0.277
< 2,500	10.3 (9.5;11.1)	9.5 (8.5;10.5)		9.5 (8.6;10.6)	
2,500 - 2,999	26.4 (25.2;27.6)	26.0 (24.6;27.5)		25.6 (24.1;27.1)	
3,000 - 3,499	38.8 (37.5;40.1)	39.0 (37.4;40.6)		38.8 (37.1;40.4)	
≥ 3,500	24.5 (23.4;25.7)	25.5 (24.0;26.9)		26.1 (24.7;27.7)	
Gestational age (weeks)			0.222		0.178
≤ 36	11.5 (10.6;12.4)	10.2 (9.2;11.3)		10.1 (9.1;11.3)	
37 - 38	20.0 (18.9;21.2)	20.1 (18.7;21.5)		20.1 (18.6;21.5)	
≥ 39	68.5 (67.1;69.8)	69.7 (68.0;71.3)		69.8 (68.1;71.4)	
Maternal schooling during pregnancy (years)			0.262		0.121
0 - 4	28.0 (26.8;29.2)	26.6 (25.2;28.1)		26.1 (24.6;27.6)	
5 - 8	46.2 (44.9;47.6)	47.9 (46.2;49.6)		48.0 (46.3;49.7)	
≥ 9	25.8 (24.6;26.9)	25.4 (24.0;26.9)		25.9 (24.4;27.4)	
Maternal smoking during pregnancy			0.590		0.406
No	66.6 (65.3;67.9)	67.2 (65.6;68.7)		67.5 (65.9;69.0)	
Yes	33.4 (32.1;34.7)	32.8 (31.3;34.4)		32.5 (31.0;34.1)	
Family income (minimum wages)			0.407		0.064
≤ 1	18.8 (17.8;19.9)	18.1 (16.8;19.4)		16.9 (15.7;18.2)	
1.1 - 3	41.8 (40.5;43.2)	41.5 (39.8;43.1)		42.1 (40.4;43.8)	
3.1 - 6	23.5 (22.3;24.6)	25.2 (23.8;26.7)		25.7 (24.2;27.2)	
6.1 - 10	8.4 (7.7;9.2)	8.0 (7.2;9.0)		8.3 (7.4;9.4)	
≥ 10	7.5 (6.8;8.2)	7.2 (6.4;8.1)		7.0 (6.2;7.9)	

[a]Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the last 12 months in the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at 22 years of age; Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the last 12 months at the 22-year follow-up.*Pearson's chi-square test; significance level of 5% - comparison between original cohort and the samples included in the analyses.

Table 2. Prevalence of obesity (BMI ≥ 30 kg/m²) and wheezing in the last 12 months at the 22-year follow-up according to demographic, socioeconomic, behavioral, and health variables in the 1993 Birth Cohort, Pelotas, Brazil.

	Obesity at 22 years of age[a] (n = 3,461)		Wheezing at 22 years of age[b] (n = 3,383)	
	% (95% CI)	p-value*	% (95% CI)	p-value*
Sex		<0.001		0.154
Male	13.7 (12.1;15.5)		10.9 (9.5;12.6)	
Female	18.5 (16.8;20.5)		9.4 (8.1;10.9)	
Skin color		0.029		0.111
White	15.0 (13.5;16.6)		9.5 (8.3;10.9)	
Black	19.1 (15.9;22.8)		12.7 (10.0;15.9)	
Other	18.2 (15.5;21.2)		10.1 (8.1;12.5)	
Maternal schooling during pregnancy (years)		0.007		0.035
0 - 4	17.4 (15.1;20.2)		11.9 (10.0;14.3)	
5 - 8	17.5 (15.7;19.5)		9.8 (8.4;11.4)	
≥ 9	12.6 (10.5;15.0)		8.9 (7.1;11.1)	
Maternal smoking during pregnancy		0.100		0.011
No	15.5 (14.1;17.1)		9.2 (8.1;10.5)	
Yes	17.8 (15.6;20.2)		12.1 (10.2;14.2)	
Family history of asthma		0.011		<0.001
No	15.1 (13.6;16.7)		7.8 (6.8;9.1)	
Yes	18.6 (16.4;21.0)		14.7 (12.8;17.0)	
Parental smoking at the 11-year follow-up		0.024		0.126
Never	13.5 (11.4;15.9)		9.1 (7.4;11.2)	
Ex-smoker	17.9 (15.5;20.6)		9.2 (7.5;11.4)	
Smoker	17.1 (15.3;19.2)		11.3 (9.8;13.1)	
Schooling at 22 years of age		0.001		<0.001
0 - 4	15.2 (8.8;24.9)		18.3 (11.3;28.1)	
5 - 8	18.5 (16.0;21.2)		14.4 (12.2;17.0)	
9 - 11	17.8 (15.8;19.9)		8.4 (7.1;10.0)	
≥ 12 years	12.1 (10.1;14.3)		8.0 (6.5;9.9)	
Asset index at 22 years of age (quintiles)		<0.001		0.020
First (poorest)	17.9 (15.1;21.1)		12.9 (10.6;15.8)	
Second	18.7 (15.8;21.9)		9.6 (7.6;12.2)	
Third	17.8 (15.1;20.1)		9.2 (7.2;11.6)	
Fourth	15.9 (13.3;18.9)		11.3 (9.1;14.0)	
Fifth (richest)	10.8 (8.6;13.5)		7.7 (5.9;10.0)	
Smoking at 22 years of age		0.080		<0.001
Never	15.4 (14.0;16.9)		7.7 (6.7;8.9)	
Ex-smoker	19.6 (15.7;24.3)		11.7 (8.7;15.5)	
Smoker	17.9 (14.9;21.3)		20.1 (16.9;23.7)	
Total physical activity ≥ 150 min/week (leisure and commuting) at age 22		0.089		0.120
No	17.7 (15.6;19.9)		9.1 (7.6;10.8)	
Yes	15.4 (13.9;17.0)		10.8 (9.5;12.2)	
Obesity (BMI ≥ 30 kg/m²) at age 22		-		0.002
No	-		9.5 (8.4;10.7)	
Yes	-		14.0 (11.3;17.2)	
Wheezing in the last 12 months at 22 years of age		0.011		-
No	15.6 (14.3;17.0)		-	
Yes	20.9 (17.0;25.5)		-	
Corticoid use in the last three months at the 22-year follow-up		0.783		<0.001
No	16.1 (14.7;17.5)		8.4 (7.4;9.5)	
Yes	16.7 (13.2;20.8)		19.3 (15.6;23.7)	
Total	16.2 (15.0;17.6)		10.1 (9.1;11.2)	

* Pearson's chi-square test or Chi-square test for linear trends. Significance level of 5%. [a] Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the last 12 months in the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at 22 years of age. [b] Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the last 12 months at the 22-year follow-up.

the prevalence of obesity in the two aforementioned categories was higher in men (13.8% and 4.7%, respectively). The same was not observed among women (Figure 1).

The association between the presence of wheezing from age 11 to 18 and obesity at 22 years of age according to sex may be observed in Table 3. There were no associations between wheezing and obesity in males. Conversely, in females, the presence of wheezing from age 11 to 18 was positively associated with obesity at 22 years of age in the crude analysis. Later, in the adjusted analyses, the wheezing category in two follow-ups maintained this association with a 95%CI that did not cross one. Women who presented wheezing in two follow-ups had 2.22 times (95%CI: 1.36; 3.61) more chances of developing obesity at 22 years of age when compared to participants who had not wheezed in previous follow-ups (p = 0.002).

In Table 4, we observed an association between obesity from 11 to 18 years of age and the presence of wheezing at age 22 according to sex. No associations were observed for males. In females, the presence of obesity in two follow-ups was positively associated with the presence of wheezing reported at 22 years of age, although without statistical significance. Female participants also showed 2.03 times (95%CI: 1.05; 3.92) greater chances of developing wheezing at age 22 than those who did not present obesity in the follow-ups of interest (p = 0.101).

DISCUSSION

The aim of this study was to analyze the bidirectional association between wheezing and obesity during adolescence and early adulthood. According to our analyses, approximately one-third of the participants presented wheezing in at least one of the adolescence follow-ups, and around 10% presented wheezing during early adulthood. On the other hand, nearly one-fifth of the participants were classified as obese in at least one follow-up between the ages of 11 and 18, and close to 16% were obese at 22. Additionally, a positive bidirectional association between wheezing and obesity was observed even after adjustment for confounding variables. In female participants, the presence of self-reported wheezing in two follow-ups between 11 and 18 years of age increased the chances of being obese at age 22. In turn, the presence of obesity in two follow-ups increased the female participants' chances of presenting wheezing at 22 years of age.

When analyzing the distribution of demographic, socioeconomic, behavioral, and health variables in participants who presented with wheezing or obesity at 22 years of age, demographic and social inequalities were observed. There was a greater prevalence of outcomes among participants with less schooling, who belonged to the poorest quintiles of the asset index, and who were of black skin color. Malta et al.[19] reported similar results when analyzing socioeconomic inequalities in the prevalence of chronic non-communicable diseases in Brazilian adults using data from the 2019 National Health Survey, reinforcing the importance of monitoring health inequality indicators and implementing public policies that address this issue.

Regarding behavioral variables, the largest prevalence of wheezing or obesity at 22 years of age was tied to the exposure category of smoking. Several studies have demonstrated positive associations between exposure to smoking and obesity or wheezing.[20,21] A meta-analysis involving 79 studies showed that exposure to smoking during pregnancy or in the

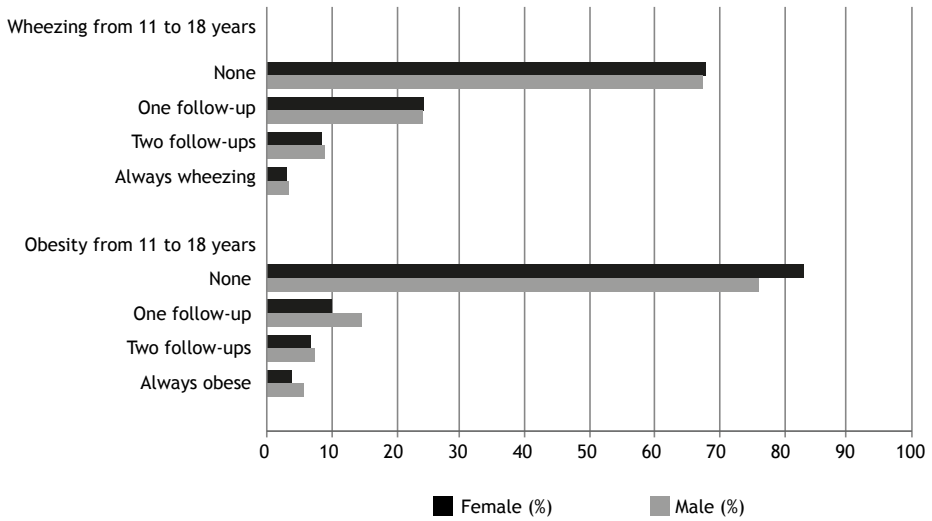

Figure 1. Prevalence of wheezing in the last 12 months and obesity during adolescence in the 1993 Birth Cohort, Pelotas, Brazil. Sample wheezing from 11 to 18 years of age: participants with information on wheezing in the 12 months prior to the follow-ups at ages 11, 15, and 18 and information on obesity (BMI ≥ 30 kg/m²) at the 22-year follow-up. Sample obesity from 11 to 18 years of age: participants with information on obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) at ages 11, 15, and 18 and information on wheezing in the 12 months prior to the 22-year follow-up.

Table 3. Association between wheezing from 11 to 18 years of age and obesity at age 22. 1993 Birth Cohort, Pelotas, Brazil.

	Obesity at 22 years of age[b]			
	Crude		Adjusted	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Wheezing from 11 to 18 years[a]				
Males (n=1,533)		0.807		0.357
None	1.00		1.00	
One follow-up	0.87 (0.59;1.28)		0.80 (0.52;1.23)	
Two follow-ups	0.98 (0.54;1.76)		0.80 (0.42;1.53)	
Always wheezing	1.10 (0.42;2.88)		0.89 (0.30;2.63)	
Females (n=1,709)		0.001		0.002
None	1.00		1.00	
One follow-up	1.34 (1.00;1.80)		1.28 (0.91;1.79)	
Two follow-ups	1.89 (1.21;2.96)		2.22 (1.36;3.61)	
Always wheezing	2.04 (0.93;4.50)		1.64 (0.68;3.99)	

OR: Odds Ratio; 95% IC: 95% confidence interval; Significance level of 5%.* p-value by Wald's test. [a] Wheezing in the 12 months prior to the follow-ups at ages 11, 15, and 18; [b] Obesity: BMI ≥ 30 kg/m². Adjusted by skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, family income at 11 years of age, parental smoking at the 11-year follow-up.

Table 4. Association between obesity from 11 to 18 years of age and wheezing at age 22. 1993 Birth Cohort, Pelotas, Brazil.

	Wheezing at 22 years of age[b]			
	Crude		Adjusted	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Obesity from 11 to 18 years[a]				
Males (n=1,545)		0.553		0.308
None	1.00		1.00	
One follow-up	0.87 (0.51;1.47)		0.88 (0.49;1.56)	
Two follow-ups	1.03 (0.50;2.12)		1.33 (0.61;2.90)	
Always obese	1.44 (0.69;2.99)		1.55 (0.70;3.40)	
Females (n=1,708)		0.054		0.101
None	1.00		1.00	
One follow-up	1.56 (0.92;2.64)		1.41 (0.77;2.58)	
Two follow-ups	1.88 (1.03;3.42)		2.03 (1.05;3.92)	
Always obese	1.10 (0.39;3.14)		0.98 (0.29;3.31)	

OR: Odds Ratio; 95% IC: 95% confidence interval; Significance level of 5%.* p-value by Wald's test. [a] Obesity (BMI ≥ 30 kg/m² or ≥ +2 z-scores) assessed in the follow-ups at ages 11, 15, and 18; [b] Wheezing in the 12 months prior to the 22-year follow-up. Adjusted by skin color, birthweight, gestational age, maternal schooling during pregnancy, maternal smoking during pregnancy, family history of asthma, family income at 11 years of age, parental smoking at the 11-year follow-up.

postnatal period (father, mother, or a relative) increased the risk of wheezing during childhood and adolescence.[21]

A document containing global strategies for asthma management and prevention (GINA) suggests the possibility of a phenotype for asthma, known as "asthma with obesity," since asthmatic obese individuals exhibit more severe respiratory symptoms and greater difficulty in disease control.[4] Our results showed that the largest prevalence of obesity was among participants who reported wheezing in the last 12 months and that had a family history of asthma. In addition, there was a larger prevalence of wheezing in obese participants when compared to those who were not obese.

The literature shows a possible positive association between asthma and obesity, though mostly in cross-sectional studies,[1,22,23] which are subject to reverse causality bias. Longitudinal studies are necessary to verify the direction of the association;[3,10,24] however, few studies have documented the bidirectional association, indicating that this approach needs to be further explored.[9-12,25]

In this study, we found that the presence of wheezing in two follow-ups increased the chance of being obese at 22 years of age by approximately 120% when compared to participants without wheezing (Table 3, females). Zhang et al.[12] also observed that children diagnosed with asthma in any given follow-up had 1.38 times (95%CI: 1.12; 1.71) more chances of becoming obese in the subsequent follow-up of their study when compared to children without asthma. The literature is uncertain regarding possible causal mechanisms associated with exposure to asthma and

the incidence of obesity. In general, the hypotheses point to reduced physical activity,[26] continuous use of asthma-control medication,[27] a potential metabolic disorder related to insulin and leptin resistance,[28] and exposure to smoking.[29] It should be noted that there are possible genetic factors common to both diseases associated with genes with pleiotropic effects, such as β2-adrenergic receptors (ADRB2), vitamin D (VDR), leptin (LEP), protein kinase C alpha (PRKCA), and tumor necrosis factor alpha (TNFα).[30]

Our results also showed that obesity increases the chance of the occurrence of wheezing and are supported by the longitudinal bidirectional studies with Mendelian randomization by Granell et al.[11] and Xu et al.,[9] who found that for each increment from 1 to 4.8 kg/m^2 in BMI, individuals had from 1.18 (95%CI: 1.11; 1.25) to 1.55 (95%CI: 1.16; 2.07) times greater risk of developing asthma. In general, the direction of the association from obesity to asthma has already been studied and described in the literature. Once again, the mechanisms related to the plausibility of the association are not well defined, but the literature points to systemic inflammation in obesity as a causal factor for the inflammation of the respiratory tracts and, consequently, wheezing. In other words, adipocytes would be a possible source of pro-inflammatory cytokines.[31]

In the same population included in this study, at 11 and 15 years of age, Noal et al.[2] found that the risk of persistent wheezing was 80% greater in obese adolescents when compared to those who were eutrophic at age 11, and among those who were in the upper tertile of the skinfold sum. From ages 18 to 22, Menezes et al.[3] found that obese individuals had 2 times (95%CI: 1.32; 3.03) more chances of developing wheezing at 22 years of age. The previously evaluated ages in this same cohort only referred to two follow-ups (ages 11 and 15 in Noal's study and 18 and 22 in Menezes'); it is possible that the bidirectionality observed in the present study was due to the longer period of analysis (11, 15, 18, and 22 years).

In a prospective population-based study performed with teenagers and young adults in Norway, Egan et al.[25] also found a possible positive bidirectional association between asthma and obesity. However, it was only significant for males, in which adolescents who presented with obesity had 1.80 times (95%CI: 1.02; 3.18) more chances of self-reported asthma diagnosis or symptoms in 11 years of follow-up, and adolescents who reported symptoms or diagnosis of asthma had 1.90 times (95%CI: 1.12; 3.24) greater chances of developing obesity. In our study, despite observing a statistically significant association between wheezing and obesity in females only, it is not possible to infer that sex is an effect modifier of the association, due to the lack of significance, which may be related to the sample size of the exposure categories and the power of the analysis for males; the other point is that males have a lower percentage of fat tissue than women, a fact that can distort the effect measure toward a null effect. Corroborating our findings, a meta-analysis of prospective longitudinal studies conducted by Beuther et al.[32] on overweightness, obesity, and the incidence of asthma showed that the association wasn't modified by sex.

When analyzing the effect measurements between the exposure categories for wheezing and obesity from ages 11 to 18, in some cases there was an increase in the effect measurement values as the exposure increased. However, it is not possible to state that there were dose-response effects in all tested associations. Meanwhile, a meta-analysis of longitudinal studies showed that the incidence of asthma increased by around 50% when subjects presented with overweightness/obesity with dose-response effects.[32]

Some limitations may be pointed out in this study, such as the use of the symptom wheezing as a "proxy" for asthma diagnosis; however, in epidemiological studies with large samples, this measurement is commonly used.[16] It is possible that wheezing in the last 12 months could be subject to information bias; nevertheless, consequent underestimation would not have a substantial effect. [17] According to the SAPALDIA study (Swiss Study on Air Pollution and Lung Diseases in Adults), respiratory symptoms are reliable predictors of asthma; wheezing as a single symptom showed the best sensitivity (74.7%), negative predictive value (99.3%), and Youden index (0.62). As for the symptom combinations, the association of wheezing with two of the three symptoms (nocturnal dyspnea, chest tightness, and cough) was the best tool for diagnosing asthma.[33] Moreover, the periods between follow-ups (approximately 3 years) and the variables' evaluation time (wheezing in the last 12 months and BMI at the moment of data collection) would lead to fluctuations in outcomes, and some information may have been lost; thus, it is not possible to state that the occurrence and effect measurements were not underestimated.

On the other hand, strong points include the prospective design of 22 years of follow-up in a population-based sample. The extended follow-up period allows the cumulative effect of the exposures over the studied outcomes to be observed. The high follow-up rates, with the smallest being 22 years (approximately 75%), reduce the possibility of selection bias, confirmed by the results in Table 1.

In conclusion, this study demonstrated a possible positive bidirectional association between wheezing and obesity, with larger effect measurement values in the wheezing to obesity direction, even after adjustments for confounders. This association appears to be more evident in females and for the category presence of wheezing/obesity in two follow-ups during adolescence. Future studies should evaluate if there are any critical points for specific ages that lead to the outcomes, to clarify the still obscure aspects of this wheezing/obesity association.

REFERENCES

1. Lu KD, Billimek J, Bar-Yoseph R, Radom-Aizik S, Cooper DM, Anton-Culver H. Sex differences in the relationship between fitness and obesity on risk for asthma in adolescents. J Pediatr. 2016;176:36-42. https://doi.org/10.1016/j.jpeds.2016.05.050. PMCID: PMC5003726.
2. Noal RB, Menezes AM, Macedo SE, Dumith SC, Perez-Padilla R, Araújo CL, et al. Is obesity a risk factor for wheezing among adolescents? A prospective study in southern Brazil. J Adolesc Health. 2012;51(6):S38-S45. https://doi.org/10.1016/j.jadohealth.2012.08.016. PMCID: PMC3500686.
3. Menezes AMB, de Oliveira PD, Blumenberg C, Sanchez-Angarita E, Niño-Cruz GI, Zabert I, et al. Longitudinal association of adiposity with wheezing and atopy at 22 years: the 1993 Birth Cohort, Pelotas, Brazil. J Asthma Allergy. 2018;11:283-291. https://doi.org/10.2147/JAA.S183699. PMID: 30555245.
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2022: 1-225. Available from: www.ginasthma.org. Accessed on: 05/18/2022.
5. Deng X, Ma J, Yuan Y, Zhang Z, Niu W. Association between overweight or obesity and the risk for childhood asthma and wheeze: An updated meta-analysis on 18 articles and 73 252 children. Pediatr Obes. 2019;14(9):e12532. https://doi.org/10.1111/ijpo.12532. PMID: 31033249.
6. Miethe S, Karsonova A, Karaulov A, Renz H. Obesity and asthma. J Allergy Clin Immunol. 2020;146(4):685-693. https://doi.org/10.1016/j.jaci.2020.08.011. PMID: 33032723.
7. Lang JE. Obesity and childhood asthma. Curr Opin Pulm Med. 2019;25(1):34-43. https://doi.org/10.1097/MCP.0000000000000537. PMID: 33032723.
8. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet. 2018;391(10118):350-400. https://doi.org/10.1016/S0140-6736(17)30879-6. Epub 2017 Sep 11. PMID: 28911920.
9. Xu S, Gilliland FD, Conti DV. Elucidation of causal direction between asthma and obesity: a bi-directional Mendelian randomization study. Int J Epidemiol. 2019;48(3):899-907. https://doi.org/10.1093/ije/dyz070. PMID: 31005996.
10. Chen YC, Fan HY, Huang YT, Huang SY, Liou TH, Lee YL. Causal relationships between adiposity and childhood asthma: bi-directional Mendelian Randomization analysis. Int J Obes (Lond). 2019;43(1):73-81. https://doi.org/10.1038/s41366-018-0160-8. PMID: 30026589.
11. Granell R, Henderson AJ, Evans DM, Smith GD, Ness AR, Lewis S, et al. Effects of BMI, fat mass, and lean mass on asthma in childhood: a Mendelian randomization study. PLoS Med. 2014;11(7):e1001669. https://doi.org/10.1371/journal.pmed.1001669. PMID: 24983943.
12. Zhang Y, Chen Z, Berhane K, Urman R, Chatzi VL, Breton C, et al. The dynamic relationship between asthma and obesity in schoolchildren. Am J Epidemiol. 2020;189(6):583-591. https://doi.org/10.1093/aje/kwz257. PMID: 31712801.
13. Victora CG, Barros FC, Halpern R, Menezes AMB, Horta BL, Tomasi E, et al. Longitudinal study of the mother and child population in an urban region of southern Brazil, 1993: methodological aspects and preliminary results. Rev Saude Publica. 1996;30(1):34-45. https://doi.org/10.1590/S0034-89101996000100005.
14. Gonçalves H, Assunção MC, Wehrmeister FC, Oliveira IO, Barros FC, Victora CG, et al. Cohort profile update: The 1993 Pelotas (Brazil) birth cohort follow-up visits in adolescence. Int J Epidemiol. 2014;43(4):1082-8. https://doi.org/10.1093/ije/dyu077. PMID: 24729426.
15. Gonçalves H, Wehrmeister FC, Assunção MCF, Tovo-Rodrigues L, Oliveira IO, Murray J, et al. Cohort Profile Update: The 1993 Pelotas (Brazil) Birth Cohort follow-up at 22 years. Int J Epidemiol. 2018;47(5):1389-1390e. https://doi.org/10.1093/ije/dyx249. PMID: 29240909.
16. Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. Clin Exp Allergy. 1998;28(5):52-66. https://doi.org/10.1046/j.1365-2222.1998.028s5052.x. PMID: 9988448.
17. Solé D, Vanna AT, Yamada E, Rizzo MC, Naspitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. J Investig Allergol Clin Immunol. 1998;8(6):376-382. PMID: 10028486.
18. Ayvas G, Çimen AR. Methods for body composition analysis in adults. The Open Obesity Journal. 2011; 3:62-9. https://doi.org/10.2174/1876823701103010062.
19. Malta DC, Bernal RTI, Lima MG, Silva AGD, Szwarcwald CL, Barros MBA. Socioeconomic inequalities related to noncommunicable diseases and their limitations: National Health Survey, 2019. Rev Bras Epidemiol. 2021;24(2):e210011. https://doi.org/10.1590/1980-549720210011.supl.2. PMID: 34910065.
20. Poorolajal J, Sahraei F, Mohamdadi Y, Doosti-Irani A, Moradi L. Behavioral factors influencing childhood obesity: a systematic review and meta-analysis. Obes Res Clin Pract. 2020;14(2):109-118. https://doi.org/10.1016/j.orcp.2020.03.002. PMID: 32199860.
21. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129(4):735-44. https://doi.org/10.1542/peds.2011-2196. PMID: 22430451.
22. Forno E, Han YY, Libman IM, Muzumdar RH, Celedón JC. Adiposity and asthma in a nationwide study of children and adults in the United States. Ann Am Thorac Soc. 2018;15(3):322-330. https://doi.org/10.1513/AnnalsATS.201709-723OC. PMID: 29144884.
23. Myung J, Lee H, Kim TH, Han E. Relationships between self-reported asthma and pulmonary function and various measures of obesity. J Asthma. 2018;55(7):741-749. https://doi.org/10.1080/02770903.2017.1362701. PMID: 28800274.
24. Lang JE, Bunnell HT, Hossain MJ, Wysocki T, Lima JJ, Finkel TH, et al. Being overweight or obese and the development of asthma. Pediatrics. 2018;142(6):e20182119. https://doi.org/10.1542/peds.2018-2119. PMID: 30478238.
25. Egan KB, Ettinger AS, DeWan AT, Holford TR, Holmen TL, Bracken MB. Longitudinal associations between asthma and general and abdominal weight status among Norwegian adolescents and young adults: the HUNT Study. Pediatr Obes. 2015;10(5):345-52. https://doi.org/10.1111/ijpo.271. PMID: 25405952.
26. Ritz T, Rosenfield D, Steptoe A. Physical activity, lung function, and shortness of breath in the daily life of individuals with asthma. Chest. 2010;138(4):913-8. https://doi.org/10.1378/chest.08-3073. PMID: 20472861.
27. Schwarzer G, Bassler D, Mitra A, Ducharme FM, Forster J. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Cochrane Database Syst Rev. 2004;2004(1):CD001384. https://doi.org/10.1002/14651858.CD001384.pub2. PMID: 14973969.
28. Arshi M, Cardinal J, Hill RJ, Davies PS, Wainwright C. Asthma and insulin resistance in children. Respirology. 2010;15(5):779-84. https://doi.org/10.1111/j.1440-1843.2010.01767.x. PMID: 20456670.
29. Riedel C, Schönberger K, Yang S, Koshy G, Chen YC, Gopinath B, et al. Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking—a meta-analysis. Int J Epidemiol. 2014;43(5):1593-606. https://doi.org/10.1093/ije/dyu150. PMID: 25080528.
30. Danielewicz H. What the genetic background of individuals with asthma and obesity can reveal: is β2-adrenergic receptor gene polymorphism important? Pediatr Allergy Immunol Pulmonol. 2014;27(3):104-10. https://doi.org/10.1089/ped.2014.0360. PMID: 25276484.
31. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol. 2005;115(5):911-9. https://doi.org/10.1016/j.jaci.2005.02.023. PMID: 15867843.
32. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007;175(7):661-6. https://doi.org/10.1164/rccm.200611-1717OC. PMID: 17234901.
33. Sistek D, Tschopp JM, Schindler C, Brutsche M, Ackermann-Liebrich U, Perruchoud AP, et al. Clinical diagnosis of current asthma: predictive value of respiratory symptoms in the SAPALDIA study. Swiss Study on Air Pollution and Lung Diseases in Adults. Eur Respir J. 2001;17(2):214-9. https://doi.org/10.1183/09031936.01.1720214. PMID: 11334122.

J Bras Pneumol. 2022;48(6):e20220265
https://dx.doi.org/10.36416/1806-3756/e20220265

ORIGINAL ARTICLE

Clinical characteristics and outcomes of incident cases of COVID-19 in unvaccinated adult cystic fibrosis patients in southern Brazil: a prospective cohort study conducted during the first year of the COVID-19 pandemic

Cristiane Christ Camargo[1,2], Letícia Bauer Jacobsen[3], Jaqueline Wilsmann[3], Michelle Nunes Silveira[1,2], Bruna Ziegler[1,2], Elis de Pellegrin Rossi[1], Carla Tatiana Oliveira[1], Paulo de Tarso Roth Dalcin[1,2]

1. Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
3. Faculdade de Nutrição, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

Submitted: 19 July 2022.
Accepted: 12 September 2022.

Study carried out at the Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: There is still limited information on the clinical characteristics and outcomes of cystic fibrosis (CF) patients with COVID-19 in Brazil. The objective of this study was to describe the cumulative incidence of COVID-19 in CF patients, as well as their clinical characteristics and outcomes. **Methods:** This was a prospective cohort study involving unvaccinated adult CF patients and conducted during the first year of the SARS-CoV-2 pandemic in the city of Porto Alegre, in southern Brazil. The clinical course of the disease was rated on the WHO Ordinal Scale for Clinical Improvement. The primary outcome was the number of incident cases of COVID-19. **Results:** Between April 30, 2020 and April 29, 2021, 98 CF patients were included in the study. Seventeen patients were diagnosed with COVID-19. For the CF patients, the annual cumulative incidence of COVID-19 was 17.3%, similar to that for the general population, adjusted for age (18.5%). The most common symptoms at diagnosis of COVID-19 were cough (in 59%), dyspnea (in 53%), fatigue (in 53%), and fever (in 47%). Only 6 (35%) of the patients required hospitalization, and 3 (17.6%) required oxygen support. Only 1 patient required mechanical ventilation, having subsequently died. **Conclusions:** During the first year of the SARS-CoV-2 pandemic in southern Brazil, the cumulative incidence rate of COVID-19 was similar between CF patients and the general population. More than 50% of the CF patients with SARS-CoV-2 infection had a mild clinical presentation, without the need for hospital admission, and almost the entire sample recovered completely from the infection, the exception being 1 patient who had advanced lung disease and who died.

Keywords: Cystic fibrosis; COVID-19; SARS-CoV-2.

INTRODUCTION

COVID-19 emerged in the city of Wuhan, in Hubei province, China, as a pneumonia of unknown origin. In February of 2020, the WHO declared the outbreak of the novel coronavirus an international public health emergency.[1] Health outcomes of individuals infected with SARS-CoV-2 range from the lack of any symptoms to severe illness and death.[2] In addition to advanced age, suspected risk factors for developing severe illness caused by SARS-CoV-2 infection include the presence of comorbidities.[3-5]

Cystic fibrosis (CF) is a recessive genetic disease caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene, mostly affecting Caucasians and predominantly involving the lungs by impairing mucociliary airway clearance.[6,7] In patients with CF, the airways become susceptible to dramatic inflammation and chronic infection.[8] Persistent lower airway infection with inflammation is the major cause of morbidity and mortality and contributes to a decline in lung function.[7]

Pulmonary exacerbations have an impact on survival in patients with CF, reducing health-related quality of life, adversely affecting sleep and neurobehavioral performance, and increasing health care costs.[9] Pulmonary exacerbations are usually caused by bacteria that are typically associated with the disease, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*,

Correspondence to:
Cristiane Christ Camargo. Rua Ramiro Barcelos, 2350, Santa Cecília, CEP 90035-903, Porto Alegre, RS, Brasil.
Tel.: 55 51 3359-8241. E-mail: cristianeccamargo@gmail.com or cccamargo@hcpa.edu.br
Financial support: This study received financial support from the *Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre* (FIPE-HCPA, Research Incentive Fund of the Porto Alegre *Hospital de Clínicas*; Grant no. 2020-0225). LBJ is the recipient of a fellowship grant from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development) *Programa Institucional de Bolsas de Iniciação Científica* (PIBIC, Institutional Program for Young Investigator Grants) – *Universidade Federal do Rio Grande do Sul* (UFRGS, Federal University of Rio Grande do Sul; Grant no. 36257).

and *Burkholderia cepacia* complex.[10] Viruses are commonly found during respiratory exacerbations, particularly the influenza A virus, the influenza B virus, and rhinovirus.[11] In comparison with nonviral exacerbations, viral exacerbations are associated with worse severity and quality-of-life scores.[9] During the 2009 influenza A (H1N1) pandemic, infection with influenza A (H1N1) virus was associated with transient but significant morbidity in most patients with CF. In a small number of CF patients with severe lung disease, influenza was associated with respiratory deterioration, need for mechanical ventilation, and even death.[12]

Patients with CF should be considered to have an increased risk of developing severe manifestations in case of SARS-CoV-2 infection. Surprisingly, the results of studies conducted in 2020 and examining SARS-CoV-2 infection in patients with CF showed that the infection rate was lower in CF patients than in the general population.[8]

The first case of COVID-19 in Brazil was diagnosed on February 26, 2020,[13,14] and the first case of COVID-19 in the state of Rio Grande do Sul, in southern Brazil, was diagnosed on March 10, 2020.[15] There is still a lack of information on the clinical characteristics and outcomes of CF patients diagnosed with COVID-19 in Brazil.

The objective of this prospective cohort study was to describe the cumulative incidence, clinical characteristics, and outcomes of incident cases of COVID-19 in unvaccinated adult CF patients during the first year of the COVID-19 pandemic.

METHODS

Study design and population

This was a prospective study conducted between April 30, 2020 and April 29, 2021 and describing the clinical characteristics and outcomes of incident cases of COVID-19 in a cohort of 98 CF patients monitored under the auspices of the *Hospital de Clínicas de Porto Alegre* (HCPA) adult CF program. The HCPA is a tertiary care teaching hospital located in the city of Porto Alegre, which is the capital of the state of Rio Grande do Sul, in southern Brazil.

In the state of Rio Grande do Sul, the social isolation measures to limit the spread of SARS-CoV-2 were implemented on March 17, 2020. Following the implementation of the measures, all health care facilities sought ways to restrict the circulation of individuals, avoiding elective medical appointments, elective procedures, and ancillary tests. Patients being followed at the HCPA CF outpatient clinic began to be monitored by telephone consultation. A WhatsApp group including patients and health care professionals was created in order to provide health care recommendations during the COVID-19 pandemic. A health questionnaire was sent to all CF patients every two weeks in order to gather information on respiratory symptoms, complaints consistent with or diagnosis of COVID-19, use of oral antibiotics, need for emergency care, and need for hospital admission. This information was collected prospectively and monitored by the multidisciplinary health care team.

The inclusion criteria were as follows: having been diagnosed with CF on the basis of clinical features and a positive sweat chloride test (> 60 mmol/L) or, in the case of patients with a borderline sweat test, the presence of a known disease-causing mutation in each copy of the *CFTR* gene[16]; and being ≥ 17 years of age before April 30, 2020. All participating patients were monitored under the auspices of the HCPA adult CF program during the COVID-19 pandemic. The primary outcome of the study was the number of incident cases of COVID-19 over a one-year period.

Study measures and procedures

One member of our research team reviewed all patient electronic medical records at the HCPA. Data on the following variables were recorded at study entry: age; sex; ethnicity; age at CF diagnosis; presence of (homozygous or heterozygous) F508del mutation; BMI; pancreatic status; CF-related diabetes; a history of massive hemoptysis requiring bronchial artery embolization; pneumothorax; a previous diagnosis of allergic bronchopulmonary aspergillosis; CF-related liver disease; liver and/or lung transplantation; chronic infection with *P. aeruginosa*, *B. cepacia*, methicillin-susceptible *S. aureus*, methicillin-resistant *S. aureus*, and/or nontuberculous mycobacteria; and use of inhaled dornase alpha, inhaled colistimethate sodium, inhaled tobramycin, and/or oral azithromycin. In addition, the latest spirometry and six-minute walk test results were reviewed in order to record FVC, FEV_1, FEV_1/FVC, the six-minute walk distance (6MWD), and oxygen saturation. FVC and FEV_1 were expressed in liters (L) and in percentage of the predicted values for age, height, and sex.[17]

In the present study, pancreatic insufficiency was defined as the use of enzymes, whereas pancreatic sufficiency was defined as no use of enzymes. Chronic infection was defined as having three or more positive isolates during the previous 12 months. CF-related diabetes was defined as the use of insulin.

Our research team recorded patient clinical information and patient answers to the health questionnaire between April 30, 2020 and April 29, 2021, identifying the incident cases of COVID-19. The diagnostic criteria for COVID-19 were a positive RT-PCR from nasal and pharyngeal swabs, chest CT findings consistent with COVID-19, a firm clinical diagnosis of COVID-19 made in a hospital setting, or any combination of the three. By the end of the study, on April 29, 2021, none of the participating patients had been vaccinated against COVID-19. The clinical course of COVID-19 was classified in accordance with the WHO Ordinal Scale for Clinical Improvement.[18] Death was defined as a patient who died for any reason.

Ethics

The study was approved by the Research Ethics Committee of the HCPA (Protocol no. 2020-0225) and by *Plataforma Brasil* (Protocol no. 33225520400005327). Written informed consent was obtained at recruitment. The study was in accordance with international and national standards for clinical studies in humans (Declaration of Helsinki and Brazilian governmental regulation—*Plataforma Brasil*).

Sample size calculation

No sample size calculation was performed a priori. The sample size was equal to the number of incident cases of COVID-19 during the study period.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). We performed a descriptive analysis of the study variables. The normality of the data distribution was examined with quantile-quantile plots and the Shapiro-Wilk test. Qualitative data were expressed as number of cases and proportion. Quantitative data were expressed as mean ± standard deviation or median and interquartile range. Categorical comparisons were performed with the chi-square test with Yates' correction (when appropriate) or Fisher's exact test. Continuous variables were compared by means of a t-test or the Wilcoxon-Mann-Whitney test. Cumulative incidence was calculated as the number of new cases of COVID-19 divided by the total number of individuals in the population at risk for the study period (1 year), being also calculated at 6-month intervals. The annual cumulative incidence rate of COVID-19 in the state of Rio Grande do Sul was also calculated, being adjusted for age.[19] The chi-square test of independence was used in order to compare the annual cumulative incidence of COVID-19 between CF patients and the general population.

RESULTS

Of a total of 130 patients being followed under the auspices of the HCPA adult CF program, 98 were included in the study. Twelve patients declined to participate, and 20 were unable to undergo remote clinical monitoring (Figure 1). Between April 30, 2020 and April 29, 2021, 17 CF patients were diagnosed with COVID-19. Of those, 14 had positive SARS-CoV-2 RT-PCR test results and 3 had clinical symptoms consistent with COVID-19 and positive SARS-CoV-2 serology. Of those 3 patients, 2 had typical chest CT findings of COVID-19. By the end of the study, on April 29, 2021, none of the participating patients had been vaccinated against COVID-19.

The characteristics of the study participants at study entry are presented in Table 1. Most (67%) of the participating patients were female. The mean age of the patients was 29.2 ± 8.8 years, and the median age at diagnosis was 3 years. The mean BMI was 21.7 ± 2.7 kg/m^2. Twenty-one percent of the patients were homozygous for the F508del mutation, and 33% were heterozygous for the F508del mutation. Seventy-nine percent had exocrine pancreatic insufficiency, 25% had CF-related diabetes, 30% had CF-related liver disease, and 70% were chronically infected with *P. aeruginosa*. The mean percent predicted FEV_1 was 59.3 ± 25.2%, and the mean percent predicted 6MWD was 69.8 ± 13.5%. Four patients had previously undergone lung transplantation, and 1 had previously undergone liver transplantation.

In the state of Rio Grande do Sul on April 29, 2021, there were records of 1,091,191 confirmed cases of SARS-CoV-2 infection, with an age-adjusted annual cumulative incidence rate of 18.5%.[16] For the CF patients, the annual cumulative incidence was 17.3%, and the cumulative incidence for the first and second 6-month periods was 4.1% and 13.3%, respectively. We found that the annual cumulative incidence of COVID-19 was not significantly different between the patients with CF and the general population (p = 0.738). The risk of SARS-CoV-2 infection did not differ between the patients with CF and the general population (OR, 0.94; 95% CI, 0.64-1.37 vs. OR, 1.06; 95% CI, 0.75-1.50). The distribution of COVID-19 cases in the study period is presented in Figure 2.

A comparison between patients with and without COVID-19 is presented in Table 1. The BMI was lower in patients with SARS-CoV-2 infection (19.8 ± 2.5 kg/m^2) than in those without SARS-CoV-2 infection (22.1 ± 2.6 kg/m^2; p = 0.001). There was a significant difference between the proportion of F508del mutations (homozygous, heterozygous, and other mutations) between the two groups (p = 0.028), with a lower proportion of heterozygosis in patients with COVID-19. There was no difference between the groups regarding percent predicted FVC (73.9 ± 20.0% vs. 75.9 ± 22.3%; p = 0.740), percent predicted FEV_1 (60.9 ± 28.1% vs. 59.0 ± 24.7%; p = 0.779), or percent predicted 6MWD (64.4 ± 12.9% vs. 70.9 ± 13.4%;

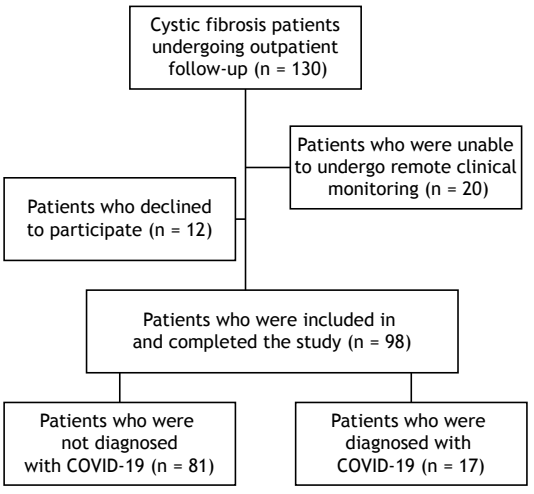

Figure 1. Flow chart of the patient selection process.

Table 1. Characteristics of the study participants at study entry and comparison between patients with and without COVID-19.[a]

Characteristic	Total	Group		p*
		COVID-19	No COVID-19	
	(N = 98)	(n = 17)	(n = 81)	
Age, years	29.2 ± 8.8	28.2 ± 9.3	29.4 ± 8.72	0.598
Sex				0.500
Male	32 (33)	2 (6)	30 (94)	
Ethnicity				1.000
White	98 (100)	17 (17.5)	81 (82.6)	
Age at CF diagnosis	3 (0-17)	8 (0-23)	3 (0-17)	0.652
BMI, kg/m^2	21.7 ± 2.7	19.8 ± 2.5	22.1 ± 2.6	0.001
F508del mutation				0.028
Homozygous	21 (21)	5 (24)	16 (76)	
Heterozygous	33 (34)	1 (3)[†]	32 (97)[†]	
Other	44 (45)	11 (25)	33 (75)	
Pancreatic insufficiency	77 (79)	12 (16)	65 (84)	0.515
CFRD	24 (25)	2 (8)	22 (92)	0.228
Pneumothorax	1 (1)	0	1 (100)	1.000
Massive hemoptysis (> 100 mL)	19 (19)	4 (21)	15 (79)	0.736
Bronchial artery embolization	8 (8)	2 (25)	6 (75)	0.624
ABPA	17 (17.3)	3 (17.6)	14 (82.4)	1.000
CF-related liver disease	28 (30)	5 (18)	23 (82)	1.000
Liver transplantation	1 (1)	0	1 (100)	1.000
Lung transplantation	4 (4)	0	4 (100)	1.000
Pseudomonas aeruginosa	67 (70)	12 (18)	55(82)	0.770
MSSA	60 (62)	11 (18)	49 (82)	0.777
MRSA	9 (9.4)	1 (11)	8 (89)	1.000
Burkholderia cepacia	22 (23)	4 (18)	18 (82)	0.757
MNT	6 (6.3)	0	6 (100)	0.585
Dornase alpha	84 (86)	13 (15.5)	71 (84.5)	0.257
Inhaled colistimethate sodium	51(52)	7 (13.7)	44 (86)	0.472
Inhaled tobramycin	33 (34)	5 (15)	28 (85)	0.899
Azithromycin	75 (76.5)	13 (17)	62 (83)	1.000
FVC, % predicted	75.5 ± 21.8	73.9 ± 20.0	75.9 ± 22.3	0.740
FEV_1, % predicted	59.3 ± 25.2	60.9 ± 28.1	59.0 ± 24.7	0.779
FEV_1/FVC, %	76.9 ± 16.1	77.5 ± 21.1	76.8 ± 15.0	0.877
SpO_2, %	94 (2.5)	95 (2.8)	94 (2.5)	0.239
6MWD, % predicted	69.81 ± 13.47	64.36 ± 12.89	70.94 ± 13.43	0.142

CF: cystic fibrosis; CFRD: cystic fibrosis-related diabetes; ABPA: allergic bronchopulmonary aspergillosis; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; NTM: nontuberculous mycobacteria; and 6MWD: six-minute walk distance. [a]Data are presented as n (%), median ± SD, or median (IQR). *Chi-square test for categorical variables. Student's t-test or Mann-Whitney U test for continuous variables. [†]Adjusted standard residual > 1.96 or < −1.96 (implies significantly different proportions).

p = 0.142). There were no differences between the groups regarding the other variables. None of the patients who had undergone lung transplantation had SARS-CoV-2 infection.

Table 2 shows the main symptoms at diagnosis of COVID-19, patient management, and respiratory support. The most common symptoms at diagnosis of COVID-19 were cough (in 59%), dyspnea (in 53%), fatigue (in 53%), fever (in 47%), and increased sputum volume (in 41%). Only 6 patients (35%) required hospitalization. Three patients (17.6%) required oxygen support during their hospital stay. Only 1 patient required ICU admission and noninvasive ventilation, followed by endotracheal intubation and mechanical ventilation. This patient died.

The WHO Ordinal Scale for Clinical Improvement for COVID-19 is shown in Figure 3. Seven patients (41%) were rated 1 (no limitation of activities), 4 (23.5%) were rated 2 (limitation of activities), 3 (17.6%) were rated 3 (hospitalized, no oxygen therapy), 2 (11.8%) were rated 4 (oxygen by mask or nasal prongs), and 1 (5.9%) was rated 8 (death). The patient who died had advanced lung disease (a percent predicted FEV_1 of 29%) and was on the waiting list for lung transplantation.

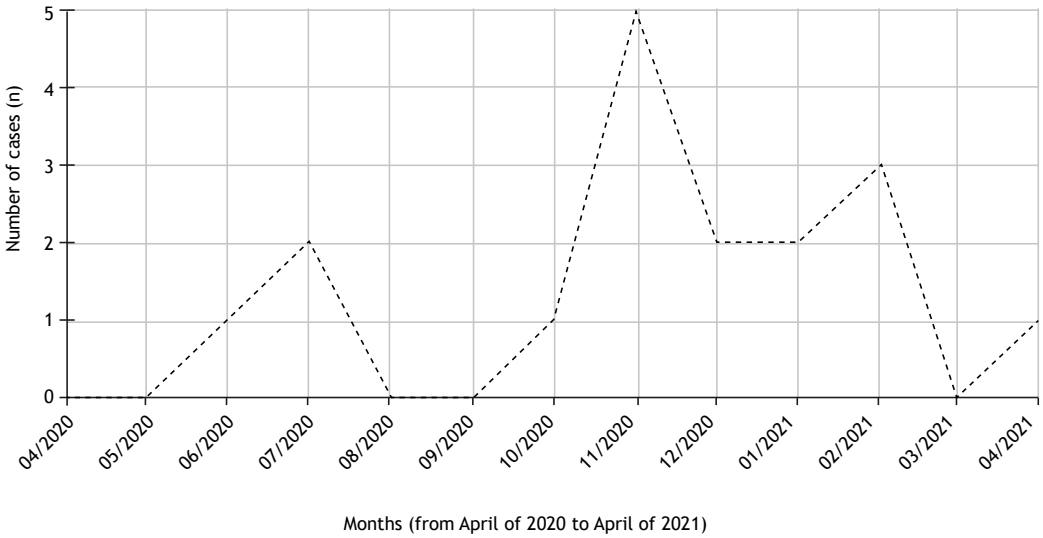

Figure 2. Distribution of COVID-19 cases during the study period.

Table 2. Main symptoms at diagnosis, patient management, and respiratory support in cystic fibrosis patients with COVID-19.

Variable	n (%)
Symptoms at diagnosis	
Fever	8 (47)
Dyspnea	9 (53)
Cough	10 (59)
Increased sputum volume	7 (41)
Fatigue and/or asthenia	9 (53)
Headache	4 (23.5)
Myalgia and/or arthralgia	4 (23.5)
Ageusia and/or anosmia	4 (23.5)
Hemoptysis	1 (5.8)
Nausea, vomiting, and/or diarrhea	4 (23.5)
Patient management	
Outpatient care	11 (64.7)
Hospitalization	6 (35)
Medical ward	5 (83)
ICU	1 (16)
Respiratory support	
Additional oxygen therapy	3 (17.6)
Noninvasive ventilation	1 (5.8)
High-flow nasal cannula oxygen therapy	0
Invasive ventilation	1 (5.8)
ECMO	0

ECMO: extracorporeal membrane oxygenation.

DISCUSSION

In this prospective cohort study performed in southern Brazil between April of 2020 and April of 2021, we described the clinical presentation and outcomes of incident cases of COVID-19 in unvaccinated adult CF patients during the first year of the SARS-CoV-2 pandemic. The cumulative incidence rate in our cohort of patients with CF was 17.3% during the study period, similar to that observed for the general population of the state of Rio Grande do Sul, which was 18.5% (adjusted for age).[19] When comparing clinical characteristics between the study participants, we found that those with COVID-19 had a lower BMI and a lower proportion of heterozygous F508del mutations than did those without COVID-19. More than 50% of the CF patients infected with SARS-CoV-2 had a mild clinical presentation, without the need for hospital admission. Almost the entire sample recovered completely from the infection, the exception being 1 patient who had advanced lung disease and who died.

Other studies have shown a lower incidence of SARS-CoV-2 infection in CF patients during the first wave than in the general population,[20-26] the incidence of SARS-CoV-2 infection being lower in the aforementioned studies than in the current study. One of the first reports on the low incidence rate of SARS-CoV-2 infection in people with CF was published by Colombo et al. on April of 2020.[20] In a multinational retrospective study, Cosgriff et al.[21] estimated that the incidence of COVID-19 in CF patients in the 15- to 57-year age bracket was 0.07%, compared with 0.15% in the general population. Between March 1 and June 30, 2020, Corvol et al.[23] conducted a large prospective study in France involving CF patients in the 9- to 60-year age bracket and found a 0.41% incidence of COVID-19, an incidence that was 93% lower than that in the general population. In a prospective multicenter cohort study conducted between February and July of 2020 and in which 50% of the patients were ≥ 18 years of age, Colombo et al.[25] reported that the cumulative incidence of SARS-CoV-2 infection was 2.4/1,000 population. However, in a retrospective study investigating the 38-country European Cystic Fibrosis Society Patient Registry, Naehrlich et al.[26] reported that the incidence of confirmed SARS-CoV-2 infection in people with CF was 2.70 cases per 1,000 population, an incidence that was not significantly different from that of SARS-CoV-2 infection in the

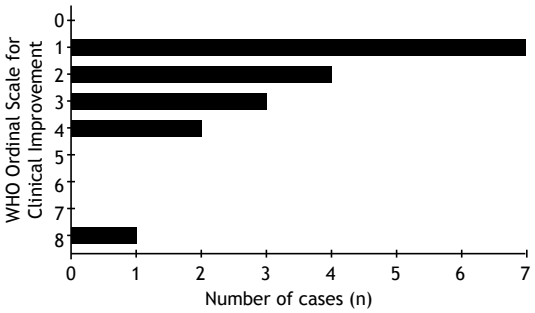

Figure 3. The World Health Organization Ordinal Scale for Clinical Improvement (for COVID-19). 0: no clinical or virological evidence of infection; 1: no limitation of activities; 2: limitation of activities; 3: hospitalized, no oxygen therapy; 4: oxygen by mask or nasal prongs; 5: noninvasive ventilation or high-flow oxygen; 6: intubation and mechanical ventilation; 7: ventilation + additional organ support (vasopressors, renal replacement therapy, or ECMO); and 8: death.

general population. When incidence was analyzed by age group, the incidence of SARS-CoV-2 infection was significantly higher in people with CF than in the general population for those under 15 years of age, those in the 15- to 24-year age bracket, and those in the 25- to 49-year age bracket.[26]

There are several possible explanations for the high cumulative incidence rate of COVID-19 in people with CF in the current study. First, testing in early 2020 was very restricted to symptomatic cases with more severe respiratory symptoms. Therefore, many cases of asymptomatic or mild infection in the general population probably went undetected. Second, people with CF may have been tested more frequently than was the general population because of increased surveillance and established care routines. Third, the current study included only adult CF patients, who usually have more severe lung disease than do younger CF patients. Consequently, adult CF patients usually take early action to treat respiratory symptoms and to be tested for SARS-CoV-2 infection. Fourth, this was a prospective study, and all patients were closely monitored with regard to their health status.

There are three CF centers in the state of Rio Grande do Sul, all of which are located in Porto Alegre (the capital of the state), and our center is the largest. In addition, the HCPA Adult CF Center is one of the largest adult CF centers in Brazil. Because almost all of the patients followed at the HCPA Adult CF Center were living in the state of Rio Grande do Sul at the time, we considered that this sample of adult CF patients was representative of the adult CF population of the state of Rio Grande do Sul.

When we compared clinical characteristics between patients, we found that those with COVID-19 had a lower BMI than did those without COVID-19. This finding is suggestive of more severe disease in patients with SARS-CoV-2 infection. Again, this could indicate that people with more severe disease usually take early action to be tested for SARS-CoV-2 infection.[26]

The study by Colombo et al.[25] compared patients who tested positive by molecular testing (cases) and those who tested negative (controls). In contrast to our study, controls were older than cases, whereas the two groups were comparable in terms of sex, *CFTR* genotype, comorbidities, CF maintenance therapy, and respiratory function prior to SARS-CoV-2 infection.

In the current study, the main symptoms at diagnosis were cough, dyspnea, fatigue/asthenia, fever, and increased sputum volume. These are consistent with the symptoms commonly experienced by the general population and with the findings reported in other cohorts of CF patients with COVID-19.[23,24,27]

The course of COVID-19 was mild in more than 50% of our patients, with only 1 patient having developed severe illness requiring ventilatory support and ICU care, and later progressing to death. Of the other patients who were hospitalized, 3 did not require any respiratory support. This is surprising given that viral infections tend to have worse outcomes in CF patients. However, it should be noted that in our study there were only 4 patients who had undergone lung transplantation and only 1 who had undergone liver transplantation. McClenaghan et al.[28] reported that 11 of the 181 individuals analyzed in their study were admitted to the ICU. Of those, 7 had undergone transplantation. A total of 7 patients died, 3 of which had undergone transplantation. Corvol et al.[23] reported that 19 of 31 patients were hospitalized, and 11 had undergone transplantation. In our cohort, none of the patients who had undergone lung or liver transplantation acquired COVID-19, and this might explain why morbidity and mortality were low in our study.

Our study has several limitations. First, the investigation was done in a single center. Second, of a total of 130 patients with CF followed at our center, only 98 were included in the study. Third, the restricted testing strategy adopted during the first phase of the COVID-19 pandemic, with only symptomatic patients being tested by PCR and limited use of serological tests, might have resulted in an underestimation of the infection rate, especially in the general population. Fourth, our study represents the situation in the first year of the COVID-19 pandemic, before COVID-19 vaccination.

In conclusion, during the first year of the SARS-CoV-2 pandemic in southern Brazil, the cumulative incidence rate of COVID-19 in CF patients was 17.3%, similar to that observed for the general population (adjusted for age), which was 18.5%. More than 50% of the CF patients with SARS-CoV-2 infection had a mild clinical presentation, without the need for hospital admission. Almost the entire sample recovered completely from the infection, the exception being 1 patient who had advanced lung disease and who died.

AUTHOR CONTRIBUTIONS

CCC: study conception and design; data collection, analysis, and interpretation; drafting of the manuscript

and tables; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. LBJ, JW, and MNS: data collection, analysis, and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. BZ: study conception and design; data analysis and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. CTMO: critical revision of the manuscript for important intellectual content; and final approval of the version to be published. EPR: data analysis and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. PTRD: study conception and design; data analysis and interpretation; drafting of the manuscript and figures; critical revision of the manuscript for important intellectual content; and final approval of the version to be published.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2021 [updated 2020 Feb 12; cited 2021 Apr 4]. COVID-19 Public Health Emergency of International Concern (PHEIC). Global research and innovation forum. Available from: https://www.who.int/publications/m/item/covid-19-public-health-emergency-of-international-concern-(pheic)-global-research-and-innovation-forum
2. Mitchell A, Chiwele I, editors. Coronavirus Disease 2019 (COVID-19). BMJ Best Practice. BMC Publishing Group; 2021.
3. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547. https://doi.org/10.1183/13993003.00547-2020
4. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy [published correction appears in JAMA. 2021 May 25;325(20):2120]. JAMA. 2020;323(16):1574-1581. https://doi.org/10.1001/jama.2020.5394
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
6. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA [published correction appears in Science 1989 Sep 29;245(4925):1437]. Science. 1989;245(4922):1066-1073. https://doi.org/10.1126/science.2475911
7. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-2531. https://doi.org/10.1016/S0140-6736(16)00576-6
8. Fainardi V, Longo F, Chetta A, Esposito S, Pisi G. Sars-CoV-2 infection in patients with cystic fibrosis. An overview. Acta Biomed. 2020;91(3):e2020035.
9. Bhatt JM. Treatment of pulmonary exacerbations in cystic fibrosis. Eur Respir Rev. 2013;22(129):205-216. https://doi.org/10.1183/09059180.00006512
10. Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med. 2009;180(9):802-808. https://doi.org/10.1164/rccm.200812-1845PP
11. Wat D, Gelder C, Hibbitts S, Cafferty F, Bowler I, Pierrepoint M, et al. The role of respiratory viruses in cystic fibrosis. J Cyst Fibros. 2008;7(4):320-328. https://doi.org/10.1016/j.jcf.2007.12.002
12. Viviani L, Assael BM, Kerem E; ECFS (A) H1N1 study group. Impact of the A (H1N1) pandemic influenza (season 2009-2010) on patients with cystic fibrosis. J Cyst Fibros. 2011;10(5):370-376. https://doi.org/10.1016/j.jcf.2011.06.004
13. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA) [homepage on the Internet]. Brasília: ANVISA [updated 2022 Jun 30 cited 2022 Jun 30]. Portos, aeroportos e fronteiras. Coronavírus. Linha do tempo. Available from: https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus/linha-do-tempo
14. Biernath A. Um ano de coronavírus no Brasil: os bastidores da descoberta do primeiro caso oficial. BBC News Brasil [homepage on the Internet]. 2021 Feb 25. Available from: https://www.bbc.com/portuguese/brasil-56189539
15. Brasil. Estado do Rio Grande do Sul. Secretaria de Vigilância em Saúde [homepage on the Internet]. Porto Alegre: Secretaria de Vigilância em Saúde; c2020 [updated 2020 Mar 10; cited 2020 Mar 10] Confirmado o primeiro caso de novo coronavírus no Rio Grande do Sul. Available from: https://saude.rs.gov.br/confirmado-o-primeiro-caso-de-novo-coronavirus-no-rio-grande-do-sul
16. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation [published correction appears in J Pediatr. 2017 May;184:243]. J Pediatr. 2017;181S:S4-S15.e1. https://doi.org/10.1016/j.jpeds.2016.09.064
17. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. https://doi.org/10.1590/S1806-37132007000400008
18. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2020 [updated 2020 Feb 18; cited 2020 Apr 22]. COVID-19 Therapeutic Trial Synopsis. Available from: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis
19. Brasil. Estado do Rio Grande do Sul. Secretaria de Vigilância em Saúde [homepage on the Internet]. Porto Alegre: Secretaria de Vigilância em Saúde; c2021 [updated 2022 Apr 12; cited 2021 Apr 29]. Boletim Epidemiológico Covid-19. Available from: https://coronavirus.rs.gov.br/informe-epidemiologico
20. Colombo C, Burgel PR, Gartner S, van Koningsbruggen-Rietschel S, Naehrlich L, Sermet-Gaudelus I, et al. Impact of COVID-19 on people with cystic fibrosis. Lancet Respir Med. 2020;8(5):e35-e36. https://doi.org/10.1016/S2213-2600(20)30177-6
21. Cosgriff R, Ahern S, Bell SC, Brownlee K, Burgel PR, Byrnes C, et al. A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis. J Cyst Fibros. 2020;19(3):355-358. https://doi.org/10.1016/j.jcf.2020.04.012
22. Bezzerri V, Lucca F, Volpi S, Cipolli M. Does cystic fibrosis constitute an advantage in COVID-19 infection?. Ital J Pediatr. 2020;46(1):143. https://doi.org/10.1186/s13052-020-00909-1
23. Corvol H, de Miranda S, Lemonnier L, Kemgang A, Reynaud Gaubert M, Chiron R, et al. First Wave of COVID-19 in French Patients with Cystic Fibrosis. J Clin Med. 2020;9(11):3624. https://doi.org/10.3390/jcm9113624
24. Mondejar-Lopez P, Quintana-Gallego E, Giron-Moreno RM, Cortell-Aznar I, Ruiz de Valbuena-Maiz M, Diab-Caceres L, et al. Impact of SARS-CoV-2 infection in patients with cystic fibrosis in Spain: Incidence and results of the national CF-COVID19-Spain survey. Respir Med. 2020;170:106062. https://doi.org/10.1016/j.rmed.2020.106062
25. Colombo C, Alicandro G, Daccó V, Gagliano V, Morlacchi LC, Casciaro R, et al. SARS-CoV-2 infection in cystic fibrosis: A

multicentre prospective study with a control group, Italy, February-July 2020. PLoS One. 2021;16(5):e0251527. https://doi.org/10.1371/journal.pone.0251527

26. Naehrlich L, Orenti A, Dunlevy F, Kasmi I, Harutyunyan S, Pfleger A, et al. Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between February and June 2020. J Cyst Fibros. 2021;20(4):566-577. https://doi.org/10.1016/j.jcf.2021.03.017

27. Mathew HR, Choi MY, Parkins MD, Fritzler MJ. Systematic review: cystic fibrosis in the SARS-CoV-2/COVID-19 pandemic. BMC Pulm Med. 2021;21(1):173. https://doi.org/10.1186/s12890-021-01528-0

28. McClenaghan E, Cosgriff R, Brownlee K, Ahern S, Burgel PR, Byrnes CA, et al. The global impact of SARS-CoV-2 in 181 people with cystic fibrosis. J Cyst Fibros. 2020;19(6):868-871. https://doi.org/10.1016/j.jcf.2020.10.003

J Bras Pneumol. 2022;48(6):e20220153
https://dx.doi.org/10.36416/1806-3756/e20220153

ORIGINAL ARTICLE

Functional status of hospitalized pediatric patients with COVID-19 in southern Brazil: a prospective cohort study

Giovana Morin Casassola[1], Caroline Jacoby Schmidt[1], Guilherme Hoff Affeldt[2], Debora Sana Morais[1], Letícia Krás Borges Alvarenga[1], Cristina Miller[1], Bruna Ziegler[1]

1. Hospital de Clínicas de Porto Alegre, Porto Alegre (RS), Brasil.
2. Programa de Pós-Graduação em Pneumologia, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS), Brasil.

Submitted: 24 August 2022.
Accepted: 27 September 2022.

Study conducted at the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul (RS), Brasil.

ABSTRACT

Objective: The present study aimed to assess the functional status of children diagnosed with COVID-19 at the time of hospitalization and the associations with clinical features. **Methods:** This prospective cohort study was carried out with children diagnosed with COVID-19 admitted to a tertiary hospital. The patients' functioning was assessed using the pediatric Functional Status Scale (FSS). **Results:** A total of 62 children with a median age of 3 years old were included in the study, and 70% had some comorbidity prior to the diagnosis of COVID-19. The median length of stay was nine days, during which period five patients died. The FSS assessment of the sample showed that approximately 55% had some functional alteration. The group of patients with the highest FSS scores presented a lengthier hospital stay ($p = 0.016$), required more oxygen therapy ($p < 0.001$), mechanical ventilation ($p = 0.001$), and intensive care unit admissions ($p = 0.019$), and had more cardiac ($p = 0.007$), neurological ($p = 0.003$), and respiratory ($p = 0.013$) comorbidities. In the multivariate analysis, there was an association between the dependent variable length of stay and the total FSS score ($\beta = 0.349$, $p = 0.004$) and the presence of comorbidities ($\beta = 0.357$, $p = 0.004$). **Conclusions:** We observed that more than half of the children hospitalized due to COVID-19 had some level of functional change. Greater alterations in functional status were associated with the presence of previous comorbidities, a greater need for ventilatory support, and longer hospital stays.

Keywords: COVID-19, coronavirus, pediatrics, physical functional performance, functional status.

INTRODUCTION

In November 2019, an outbreak of pneumonia of unknown etiology began in Wuhan, China, which was then identified as a new coronavirus, known as SARS-CoV-2.[1,2] The first cases of the disease in the pediatric population appeared at the beginning of the pandemic.[3]

Most cases of this infection in the pediatric population are asymptomatic or present with mild symptoms.[3–5] However, the presence of previous comorbidities is a risk factor for the development of severe disease.[6] Studies show that half of the COVID-19 patients admitted to intensive care units (ICU) and nearly 80% of those hospitalized had at least one comorbidity prior to admission.[4,6] Moreover, approximately 46% of pediatric patients with COVID-19 require hospitalization, and around 10% require intensive care; the mortality rate is 5.7%.[3,4,7,8]

COVID-19 has been shown to cause many aftereffects, including impairment of respiratory and muscle functions, reduced functionality, and difficulty performing daily tasks.[9,10] These changes can manifest in children as loss of motor milestones and delay in motor development.[10–12] Among the several professionals who work in the treatment of COVID-19, physical therapists are involved in the treatment, prevention, and rehabilitation of the functional changes caused by the disease. Thus, the assessment of the functional status of patients with COVID-19 at the time of hospital admission could contribute to the screening of more critically ill patients and assist in physical therapy during hospitalization.

Few studies analyze the functional profile of hospitalized children with COVID-19. The pediatric population usually shows mild symptoms of the disease, but children with previous comorbidities are more likely to develop severe cases of COVID-19, thus requiring hospitalization. Therefore, the functional profile of these children must be assessed to prepare the healthcare system for their admission, as well as intensify preventive practices and plan better physiotherapeutic strategies for adequate treatment.

Thus, the aim of the present study was to verify the prevalence of altered functioning in pediatric patients diagnosed with COVID-19 admitted to the pediatric inpatient unit of the Hospital de Clínicas de Porto Alegre (HCPA).

METHODS

A prospective cohort study was conducted in children diagnosed with COVID-19 admitted to the HCPA from

Correspondence to:
Bruna Ziegler. Rua Travessa Miranda e Castro 70/204, Bairro Santana, Porto Alegre, RS, CEP 90040-280.
Tel.: 55 (051) 99122-1192. E-mail: brunaziegler@yahoo.com.br.
Financial support: Fundo de Incentivo à Pesquisa (FIPE), HCPA.

March 2020 to June 2021. This study was approved by the Research Ethics Committee of the HCPA, under Protocol No. 48189021400005327, according to Resolution 466/2012 of the HCPA National Health Council.

The collection of clinical and sociodemographic data was performed with the aid of electronic medical records, and the analyzed variables were: date of hospital admission, ethnicity/skin color, sex, age, weight, presence of comorbidities (cardiac, respiratory, neurological, metabolic, and/or oncological), laboratory tests (C-reactive protein, d-dimers, and lymphocyte, leukocyte, and platelet counts), the need for ventilatory support (oxygen therapy, non-invasive, high-flow nasal cannula (HFNC), mechanical ventilation (NIV), and invasive mechanical ventilation (MV)), functional status assessed using the Functional Status Scale (FSS), the severity of involvement by COVID-19 (Ordinal Scale for Clinical Improvement), length of stay, and death. The latter was defined as a patient who died for any given reason.

Pediatric patients of either sex, aged less than 18 years old, with a positive result in the reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2,[13,14] who were hospitalized at the HCPA were included in the study. Those who refused to participate and cases of reinfection were excluded.

According to the institutional protocol for the management of patients with COVID-19, individuals with moderate to severe symptoms were hospitalized, as well as patients with previous comorbidities due to exacerbation of the underlying disease. Oxygen therapy was indicated for patients with peripheral oxygen saturation (SpO_2) < 93%, increased respiratory rate (RR) according to age, and/or signs of respiratory effort. In cases of SpO_2 < 93% with supplemental oxygen therapy > 5 L/min without signs of multiple organ failure, the use of an HFNC was indicated. NIV was indicated for cases of hypoxemic respiratory failure without a satisfactory response to oxygen therapy alone and/or HFNC. Patients with hemodynamic instability requiring vasoactive drugs, respiratory failure regardless of the support provided in the ward, a need for invasive MV, and other organic dysfunctions were transferred to the ICU. The criteria for the use of invasive MV were: severe acute respiratory syndrome, SpO_2 < 93% using HFNC or NIV, PaO_2/FiO_2 ratio < 200, and evident signs of respiratory distress. The criteria for hospital discharge were considered as the improvement of SpO_2 and RR to baseline levels or acceptable limits, with the stability of the patient's condition, for at least 12 hours (ideally 24 hours).

The functionality of the patients was evaluated using the pediatric FSS, which was translated and validated for the Brazilian pediatric population.[15] This scale assesses the following domains: mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status. Each domain receives a final score ranging from 1 to 5, where 1 is considered "normal" and 5, "very severe dysfunction." The total scores ranged from 6 to 30, in which the results could be categorized as adequate functionality (6–7 points), mild dysfunction (8–9 points), moderate dysfunction (10–15 points), severe dysfunction (16–21 points), and very severe dysfunction (22–30 points).[15,16] These data were collected from the physical therapy evaluations recorded in the electronic medical records of the study patients at the time of hospitalization. The evaluation of functional status is part of the standard assessment of the hospital's physical therapy service and is always performed within the first 24 hours of hospitalization. Prior to the beginning of the study, all the physical therapists involved underwent specific training.

The severity of COVID-19 was classified using the World Health Organization (WHO)'s Ordinal Scale for Clinical Improvement.[17] This scale has domains ranging from 0 to 8 points, in which the results can be categorized as not infected (0 points), outpatient follow-up (1–2 points), hospitalization with mild disease (3–4 points), hospitalization with severe disease (5–7 points), and death (8 points).

Functional status was also evaluated using the Lansky scale,[18] intended for individuals under 16 years of age, in which the patient's performance and well-being are assessed, including their ability to perform daily activities and functional capacity. The score on an ordinal scale ranges from 10 to 100, where 10 represents a child who does not get out of bed, and 100, a child who is fully active.

The sample size was calculated using the online version of the PSS Health tool.[19] The mean FSS score was estimated with a 2.5-point absolute margin of error and a 95% confidence level. Based on an expected FSS standard deviation (SD) of 8.9 points[20] (estimated from the interquartile range), the sample size was defined as 52 subjects. Considering 15% of losses, a total of 62 individuals were recruited.

All variables were expressed as number of cases (proportion), median, and interquartile range (IQR) (25 percentile and 75 percentile). The Shapiro-Wilk test was used to assess the normality of continuous variables. The individuals were classified into two groups for analysis: FSS score ≤ 9 points and FSS score ≥ 10 points. Non-parametric comparisons between groups were conducted using the Mann-Whitney U test. Spearman's correlation analysis (non-parametric data) was used for correlations between the global FSS score and other clinical variables. Univariate and multivariate linear regression were performed, considering the logarithm of length of stay as the dependent variable since it had asymmetric distribution. All data were stored in a Microsoft Office Excel 2019 spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS), version 18.0, adopting a 5% statistical significance level ($p < 0.05$).

RESULTS

A total of 62 unvaccinated children diagnosed with COVID-19 were included in the study, 39 (62.9%) of

whom were male and with a median age of 3 years old (0.4–10). Approximately 70% (n = 43) of the patients already had some comorbidity prior to the diagnosis of COVID-19. Around 8% were diagnosed with COVID-19 at the time of admission due to the underlying pathology and were asymptomatic. The median length of stay of patients was nine days (5–23); 26 patients required ventilatory support during hospitalization (41.9%), and five died (8.1%). The sample characterization data are shown in Table 1.

Table 2 shows the comparison between the groups of patients with FSS ≤ 9 points (preserved functionality or mild dysfunction) and FSS ≥ 10 points (moderate, severe, or very severe dysfunction). The group of patients with FSS ≥ 10 points had a longer hospital stay ($p = 0.016$), required more oxygen therapy ($p < 0.001$) and mechanical ventilation ($p = 0.001$), more admissions to the ICU ($p = 0.019$), and presented more cardiac ($p = 0.007$), neurological ($p = 0.003$), and respiratory ($p = 0.013$) comorbidities than children with FSS ≤ 9 points.

We found a moderately significant and positive correlation between the total FSS score and the length of hospital stay ($r = 0.607$, $p < 0.001$) and the severity of COVID-19 ($r = 0.575$, $p < 0.001$). The FSS score was also inversely correlated with the Lansky scale score ($r = -0.664$, $p < 0.001$).

Only 11 children in this sample required invasive mechanical ventilation and, consequently, used sedative analgesics and/or neuromuscular blockers. However, the functionality scale was evaluated in the first 24 hours of hospitalization, when the patients had not yet received invasive mechanical ventilation, showing no interference in the initial functionality assessment.

The univariate and multivariate linear regression data considering the dependent variable logarithm of length of stay are shown in Table 3.

DISCUSSION

In this study, we report the prevalence of functional changes in pediatric patients hospitalized with COVID-19 in a hospital in southern Brazil. In our sample, 69.4% of the patients had some comorbidity prior to COVID-19 diagnosis. The assessment via pediatric FSS showed that 53.2% of the individuals had some change in functioning, with 27.4% presenting moderate to very severe alterations. In the stratification of our data, patients with FSS ≥ 10 points had a higher prevalence of previous comorbidities (respiratory, neurological, cardiac, and metabolic), longer hospital stays, and required more ventilatory support and ICU admissions than those with FSS ≤ 9 points. In the correlation analysis, we observed a moderately significant and positive correlation of the total FSS score, the length of hospital stay, and the severity of COVID-19, and an inverse correlation with the Lansky scale score. The univariate analysis showed a significant association of length of stay, the FSS score, the presence of comorbidities, the Lansky scale score, and the severity of COVID-19. The multivariate analysis showed a significant association of length of stay, the FSS score, and the presence of comorbidities.

According to our data, the patients with greater functional changes (FSS ≥ 10 points) were the ones with the most comorbidities (83.3%). The presence of comorbidities is a risk factor for the development of more severe forms of the disease.[6] The study by Woodruff et al. (2022)[21] corroborates our findings by demonstrating that more than 50% of pediatric patients hospitalized with COVID-19 had at least one comorbidity prior to hospital admission. As observed herein, cardiac, respiratory, oncological, and neurological comorbidities are the most prevalent in the literature.[21,22]

Most of the evaluated sample had at least one comorbidity before the diagnosis and hospitalization for COVID-19. Despite no prior assessment, the changes in functionality found at hospital admission may relate to the presence of previous comorbidities. Other studies suggest that patients with chronic diseases have impaired functioning, motor performance, and independence.[23,24] Kolman et al. (2018)[25] demonstrated that functional status and mobility are predictors of health and quality of life in neurological patients.

Our study showed that the group of patients with FSS ≥ 10 points had a longer duration of hospital stay. The length of stay at the hospital relates to the presence of previous chronic pathologies, as patients with comorbidities require more healthcare assistance.[26] According to the literature, the length of hospital stay in pediatric patients with COVID-19

Table 1. Characterization of the individuals hospitalized with COVID-19.

Characteristics	n = 62
Male	39 (62.9%)
White	51 (82.3%)
Age (years)	3.0 (0.4-10)
SpO_2 admission	98.5 (96-100)
FiO_2 admission	21 (21-21)
Length of Stay (days)	9 (5-23)
Comorbidities	43 (69.4%)
Asymptomatic	5 (8.1%)
Ventilatory Support	26 (41.9%)
Functional Status Scale	
Adequate Functionality	28 (45.2%)
Mild Dysfunction	16 (25.8%)
Moderate Dysfunction	14 (22.6%)
Severe Dysfunction	1 (1.6%)
Very Severe Dysfunction	2 (3.2%)
Ordinal Scale for Clinical Improvement (points)	4 (3-5)
Lansky Scale (points)	70 (40-85)
Deaths	5 (8.1%)

Data were expressed as n (%) or median (25 percentile –75 percentile). n = number of cases; SpO_2 = oxygen saturation; FiO_2 = fraction of inspired oxygen.

Table 2. Comparison of the sample of pediatric individuals hospitalized with COVID-19 according to the presence of changes in functionality by the FSS.

Characteristics	FSS ≤ 9 points n = 44	FSS ≥ 10 points n = 17	p
Male	26 (59.1%)	13 (76.5%)	0.562
Weight (kg)	12,1 (6.4-36)	11.88 (6.9-21.9)	0.794
Age (years)	2 (0.4-10)	2.5 (0.4-9)	0.924
SpO_2 admission, %	99 (97-100)	98 (94-100)	0.487
FiO_2 admission, %	21 (21-21)	21 (21-28)	0.122
PaO_2/FiO_2 admission	161.5 (94.5-288.1)	109.9 (72.8-173.2)	0.346
Length of Stay (days)	7.5 (5-14)	21.5 (7-40)	0.016
Comorbidities	28 (63.6%)	15 (88.2%)	0.265
Cardiac Comorbidity	1 (2.3%)	5 (29.4%)	0.007
Respiratory Comorbidity	5 (11.4%)	8 (47.1%)	0.013
Neurological Comorbidity	4 (9.1%)	8 (47.1%)	0.003
Metabolic Comorbidity	6 (13.6%)	5 (29.4%)	0.275
Oncological Comorbidity	11 (25%)	1 (5.9%)	0.089
Immunosuppression	7 (15.9%)	1 (5.9%)	0.417
Tracheostomy	0 (0%)	4 (23.5%)	0.006
Ventilatory Support			
Oxygen Therapy	17 (38.6%)	17 (100%)	<0.001
HFNC	7 (15.9%)	6 (35.3%)	0.176
NIV	3 (6.8%)	4 (23.5%)	0.180
MV	3 (6.8%)	8 (47.1%)	0.001
ICU admission	11 (25%)	11 (64.7%)	0.019
Clinical laboratory tests			
CRP	13.8 (1.8-54.9)	41.1 (7.3-112.9)	0.328
D-dimers	1.4 (0.6-2.2)	1.1 (0.6-3.6)	0.957
Lymphocytes	3.4 (1.9-6.4)	2.1 (0.8-3.1)	0.144
Leukocytes	9 (5.5-11.7)	7.8 (5.6-11.7)	0.816
Platelets	289 (192-418)	229 (143-326)	0.337
Deaths	3 (6.8%)	2 (11.8%)	0.616

Data were expressed as n (%) or median (25 percentile - 75 percentile). FSS = Functional Status Scale; n = number of cases; kg = kilograms; SpO_2 = oxygen saturation; FiO_2 = fraction of inspired oxygen; PaO_2 = oxygen blood pressure; HFNC = high-flow nasal cannula; NVI = non-invasive ventilation; MV = mechanical ventilation; ICU = intensive care unit; CRP = C-reactive protein.

Table 3. Univariate and multivariate linear regression analyses considering the dependent variable length of stay (logarithm).

Characteristics	Univariate			Multivariate		
	β	CI	p	β	CI	p
FSS, points	0.397	0.036-0.159	0.002	0.349	0.028-0.143	0.004
Comorbidities	0.404	0.313-1.323	0.002	0.357	0.246-1.200	0.004
Lansky scale, points	-0.406	-0.024-0.006	0.002	-	-	-
Ordinal Scale for Clinical Improvement, points	0.327	0.055-0.460	0.014	-	-	-

β = linear regression coefficient; CI = confidence interval.

ranges from 1 to 20 days and shows less than 35% presence of comorbidities.[27–29] The longer length of stay in our study may be due to the higher prevalence of comorbidities and the complexity of our sample.

The study by Pollack et al., in 2009,[16] evidenced that higher FSS scores at the time of hospital admission correlate with longer hospital stays and increased use of mechanical ventilation. In addition, patients with higher scores at discharge tend to have worse clinical outcomes in the subsequent three years.[30] Thus, the assessment of the functional status of pediatric patients with COVID-19 during hospitalization can be considered a useful instrument that can assist in the physical therapy of groups at higher risk.

The group of children with FSS ≥ 10 points required more oxygen therapy, high-flow nasal cannula support, non-invasive mechanical ventilation, and invasive mechanical ventilation. Similar to other studies, few cases of children have progressed to the severe form of COVID-19. However, the presence of comorbidities

is an incisive factor and is present in most patients who require ventilatory support and ICU hospitalization.[3,31–33]

The role of COVID-19 in the functional changes of children remains unclear, as many children had previous comorbidities that contributed to such alterations. The need for ICU admission can also be associated with comorbidities and complex medical histories.[34] COVID-19 can exacerbate a coexisting chronic disease or be an additional factor in a patient's severe clinical course, as well as alter their functionality. Therefore, the influence of comorbidities and SARS-CoV-2 infection on the clinical outcome may be combined.[28]

This study prospectively evaluated hospitalized children diagnosed with COVID-19 for one year and four months. It was conducted at a single center, which may limit the generalization of its findings to different populations. Additional studies are necessary to identify long-term outcomes, as are multicenter studies involving larger sample sizes. We did not assess the use of medications due to the heterogeneity of the analyzed sample. This can be considered a limitation of the study, as some drugs can influence some domains of the functional status scale. Despite these limitations, our study is one of the pioneers in the evaluation of the functioning of pediatric patients diagnosed and hospitalized with COVID-19 in Brazil.

In conclusion, functional changes were found in approximately 53% of the pediatric patients hospitalized with COVID-19 in a hospital in southern Brazil. Greater alterations in functional status were associated with the presence of previous comorbidities, greater need for ventilatory support, and longer hospital stays. The FSS is essential to assess the functional status of pediatric patients hospitalized with COVID-19 since it is validated for the Brazilian population, simple to apply, and crucial to assist in physical therapy management.

AUTHOR CONTRIBUTIONS

Literature search: GMC, CJS, GHA, DSM, LKBA, CM, and BZ; data collection: GMC, CJS, GHA, and BZ; study design: GMC, CJS, DSM, LKBA, CM, and BZ; data analysis: GMC, CJS, and BZ; manuscript preparation: GMC, CJS, GHA, DSM, LKBA, CM, and BZ; manuscript review: DSM, LKBA, CM, and BZ.

ACKNOWLEDGMENTS

The authors would like to thank all study collaborators and participants. Funding was obtained through the Fundo de Incentivo à Pesquisa (FIPE) of the Hospital de Clínicas de Porto Alegre.

REFERENCES

1. Du H, Dong X, Zhang J-J, Cao Y-Y, Akdis M, Huang P-Q, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. Allergy. 2021;76(2):510-532. https://doi.org/10.1111/all.14452.
2. Su L, Ma X, Yu H, Zhang Z, Bian P, Han Y, et al. The different clinical characteristics of corona virus disease cases between children and their families in China – the character of children with COVID-19. Emerg Microbes Infect. 2020;9(1):707-713. https://doi.org/10.1080/22221751.2020.1744483.
3. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Tong S. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702. https://doi.org/10.1542/peds.2020-0702.
4. Bailey LC, Razzaghi H, Burrows EK, Bunnell HT, Camacho PEF, Christakis DA, et al. Assessment of 135794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 across the United States. JAMA Pediatr. 2021;175(2):176-184. https://doi.org/10.1001/jamapediatrics.2020.5052.
5. Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. J Clin Virol. 2020;128:104395. https://doi.org/10.1016/j.jcv.2020.104395.
6. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA Pediatr. 2020;174(9):868-873. https://doi.org/10.1001/jamapediatrics.2020.1948.
7. Sena GR, Lima TPF, Vidal SA, et al. Clinical characteristics and mortality profile of COVID-19 patients aged less than 20 years old in Pernambuco – Brazil. Am J Trop Med Hyg. 2021;104(4):1507-1512. https://doi.org/10.4269/ajtmh.20-1368.
8. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine. 2020;24:100433. https://doi.org/10.1016/j.eclinm.2020.100433.
9. da Silva e Silva CM, do Nascimento Andrade A, Nepomuceno B, et al. Evidence-based physiotherapy and functionality in adult and pediatric patients with COVID-19. J Hum Growth Dev. 2020;30(1). https://doi.org/10.7322/JHGD.V30.10086.
10. Schaan CW, Vieira VS, Miller C, Peiter APD, Piccoli T, Cavion G, et al. Hospital physical therapy management in pediatric patients with COVID-19: Case reports. Rev Paul Pediatr. 2020;39:e2020238. https://doi.org/10.1590/1984-0462/2021/39/2020238.
11. Pinto TF, Carvalho CRF. SARS CoV-2 (COVID-19): lessons to be learned by Brazilian Physical Therapists. Braz J Phys Ther. 2020;24(3):185-186. https://doi.org/10.1016/j.bjpt.2020.04.004.
12. Boswell L, Weck M, Hayner A, Fjørtoft T, Støen R, Adde L, et al. The impact of prolonged hospitalization on infant motor development compared with healthy controls. Dev Med Child Neurol. 2015;57(S5):79-80. https://doi.org/10.1111/dmcn.8_12886.
13. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469. https://doi.org/10.1038/s41586-020-2196-x.
14. Badal S, Thapa Bajgain K, Badal S, Thapa R, Bajgain BB, Santana MJ. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. J Clin Virol. 2021;135:104715. https://doi.org/10.1016/j.jcv.2020.104715.
15. Bastos VCS, Carneiro AAL, Barbosa MDSR, Andrade LB. Brazilian version of the Pediatric Functional Status Scale: Translation and cross-cultural adaptation. Rev Bras Ter Intensiva. 2018;30(3):301-307. https://doi.org/10.5935/0103-507X.20180043.
16. Pollack MM, Holubkov R, Glass P, Dean JM, Meert KL, Zimmerman J, et al. Functional status scale: New pediatric outcome measure. Pediatrics. 2009;124(1):e18-28. https://doi.org/10.1542/peds.2008-1987.
17. World Health Organization. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. World Heal Organ. 2020;(February 18, 2020, Geneva, Switzerland).
18. Lansky LL, List MA, Lansky SB, Cohen ME, Sinks LF. Toward the development of a play performance scale for children (PPSC). Cancer. 1985;56(7 Suppl):1837-1840. https://doi.org/10.1002/1097-0142(19851001)56:7+<1837::AID-CNCR2820561324>3.0.CO;2-Z.
19. Borges RB, Mancuso ACB, Camey SA, Leotti VB, Hirakata VN, Azambuja GS, et al. Power and Sample Size for Health Researchers: a tool for calculating sample size and statistical power designed for health researchers. Clin Biomed Res. 2020;40(4):247-253. https://doi.

org/10.22491/2357-9730.109542.

20. Pereira GA, Schaan CW, Ferrari RS. Functional evaluation of pediatric patients after discharge from the intensive care unit using the Functional Status Scale. Rev Bras Ter Intensiva. 2017;29(4):460-465. https://doi.org/10.5935/0103-507X.20170066.
21. Woodruff RC, Campbell AP, Taylor CA, Chai SJ, Kawasaki B, Meek J, et al. Risk Factors for Severe COVID-19 in Children. Pediatrics. 2022;149(1):e2021053418. https://doi.org/10.1542/peds.2021-053418.
22. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020;146(4):e2020009399. https://doi.org/10.1542/peds.2020-009399.
23. Netto ART, Wiesiolek CC, Brito PM, Rocha GA da, Tavares RMF, Lambertz KMF. Functionality, school participation and quality of life of schoolchildren with cerebral palsy. Fisioter Mov. 2020;33. https://doi.org/10.1590/1980-5918.033.ao29.
24. Camargos ACR, Lacerda TTB de, Barros TV, Silva GC da, Parreiras JT, Vidal TH de J. Relationship between functional independence and quality of life in cerebral palsy. Fisioter Mov. 2012;25(1). https://doi.org/10.1590/s0103-51502012000100009.
25. Kolman SE, Glanzman AM, Prosser L, Spiegel DA, Baldwin KD. Factors that Predict Overall Health and Quality of Life in Non-Ambulatory Individuals with Cerebral Palsy. Iowa Orthop J. 2018;38:147-152. PMID: 30104938. PMCID: PMC6047378.
26. Hudson SM. Hospital readmissions and repeat emergency department visits among children with medical complexity: an integrative review. J Pediatr Nurs. 2013;28(4):316-339. https://doi.org/10.1016/j.pedn.2012.08.009.
27. Gonçalves ALN, Feitoza AC, Albuque LJV, Falcão ACAM, Rocha MAW, Novais DMGA, et al. COMORBIDADES ASSOCIADAS EM PACIENTES PEDIÁTRICOS POSITIVOS COM COVID-19. Braz J Infect Dis. 2021;25:101104. https://doi.org/10.1016/j.bjid.2020.101104.
28. Mania A, Pokorska-Śpiewak M, Figlerowicz M, Pawłowska M, Mazur-Melewska K, Faltin K, et al. Pneumonia, gastrointestinal symptoms, comorbidities, and coinfections as factors related to a lengthier hospital stay in children with COVID-19—analysis of a paediatric part of Polish register SARSTer. Infect Dis (Lond). 2022;54(3):196-204. https://doi.org/10.1080/23744235.2021.1995628.
29. Nallasamy K, Angurana SK, Jayashree M, Mathew JL, Bansal A, Singh MP, et al. Clinical Profile, Hospital Course and Outcome of Children with COVID-19. Indian J Pediatr. 2021;88(10):979-984. https://doi.org/10.1007/s12098-020-03572-w.
30. Pinto NP, Rhinesmith EW, Kim TY, Ladner PH, Pollack MM. Long-Term Function after Pediatric Critical Illness: Results from the Survivor Outcomes Study. Pediatr Crit Care Med. 2017;18(3):e122-e130. https://doi.org/10.1097/PCC.0000000000001070.
31. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci. 2020;50(SI-1):592-603. https://doi.org/10.3906/SAG-2004-174.
32. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr. 2020;16(3):240-246. https://doi.org/10.1007/s12519-020-00345-5.
33. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls - NCBI Bookshelf. 2020.
34. Pathak EB, Salemi JL, Sobers N, Menard J, Hambleton IR. Covid-19 in children in the United States: Intensive care admissions, estimated total infected, and projected numbers of severe pediatric cases in 2020. J Public Health Manag Pract. 2020;26(4):325-333. https://doi.org/10.1097/PHH.0000000000001190.

J Bras Pneumol. 2022;48(6):e20210360
https://dx.doi.org/10.36416/1806-3756/e20210360

ORIGINAL ARTICLE

Risk prediction for Obstructive Sleep Apnea prognostic in Obese patients referred for bariatric surgery

Adriana Fontes Hora[1], Lara Maris Nápolis[1], Débora Strose Villaça[1], Renata dos Santos[1], Thales Delmondes Galvão[1], Sonia Maria Guimarães Togeiro[1], Lia Rita Bittencourt[1], Luiz Eduardo Nery[1]

1. Departamento de Pneumologia, Universidade Federal de São Paulo, São Paulo (SP), Brasil.

Submitted: 27 September 2021.
Accepted: 07 September 2022.

Study carried out in the a private clinic in the city of São Paulo, (SP), Brasil.

ABSTRACT

Objectives: (i) To assess the anthropometric measurements, along with the clinical characteristics and quality of life profiles of the studied patients; (ii) To determine the occurrence and severity of Obstructive Sleep Apnea (OSA), using polysomnography; and (iii) To identify the best anthropometric and clinical indicators to predict OSA in obese patients who are candidates for bariatric surgery. **Methods:** a prospective observational study conducted in a private clinic, using consecutive sampling of patients eligible for bariatric surgery with a BMI ≥ 40, or with a BMI of ≥ 35 kg/m² accompanied by comorbidities associated with obesity. **Results:** Sixty patients were initially selected, of whom 46 agreed to take part in the preoperative evaluation. OSA was observed in 76% of patients, 59% of whom had moderate-to-severe OSA, with a predominance of men in these groups. Among the variables suggesting statistical difference between groups, waist-to-hip ratio (WHR) was the only clinical factor associated with scores the apnea hypopnea index (AHI) ≥ 15, with a cut-off value of 0.95. The results showed that patients scoring above 0.95 are three times more likely to have moderate-to-severe apnea. **Conclusion:** The best risk factor for the prognostic of moderate-to-severe OSA was presenting a WHR score with a cut-off value of 0.95 or above.

Keywords: Obstructive sleep apnea; Bariatric surgery; Anthropometry; Waist-to-hip ratio.

INTRODUCTION

Obesity is considered one of the top ten public health problems in the world by the World Health Organization (WHO), and it is described as an increasingly frequent disease, with its prevalence tripling in the last 40 years, affecting around 13% of the world's adult population, and 18.9% of adults in Brazil.[1,2]

This rise in the occurrence of obesity is related to an increase of other comorbidities, including the obstructive sleep apnea (OSA), presenting a well-established causal association. Obesity and OSA are exceptionally common health problems, characterized by the disturbance of glucose homeostasis, insulin resistance, hypercholesterolemia and hyperlipidemia[3-6]. OSA is strongly associated with visceral adiposity, and both conditions are related to cardiovascular as well as with metabolic complications.[7,8] In an epidemiological study (EPISONO) conducted with a representative sample comprised of adults from the capital of São Paulo, Brazil, OSA was found in 32.8% of the target population.[9]

Among the various therapeutic options for patients with severe obesity, the metabolic and bariatric surgery (MBS) is a both restrictive and malabsorptive procedure, and it can lead to significant weight loss as well as modulate the patient's metabolic profile.[10] Several studies have shown that the prevalence of OSA in individuals who are candidates for MBS is higher than in the general population[11-13]. However, it is not known whether the occurrence of OSA in a population composed of predominantly young individuals seeking this type of private treatment in São Paulo differs from that described in the literature regarding the general population.

Although polysomnography (PSG) is the gold standard test for diagnosing OSA[14] in clinical practice, it is not always possible to apply it to all subjects, either because of the cost, or the availability of services able to perform a high-quality PSG test. Thus, it is necessary to gather clinical and anthropometric data for patient stratification regarding high risk of OSA, for the referral of PSG. In the reviewed literature, no measures or criteria that could meet this objective have been described as yet. That being said, neck and abdominal circumference measurements as well as waist-to-hip ratio have been suggested in previous studies as assessment strategies alternative to using only BMI, but without determining a specific cut-off value for this purpose.[3,15-17] Although

Correspondence to:
Adriana Fontes Hora. Universidade Federal de São Paulo, Rua Coronel Lisboa, 966, Vila Clementino, CEP 04039-002, São Paulo, SP, Brasil.
Tel.: +55 (11) 5576-4848 voip 1494. E-mail: hdri21@yahoo.com.br
Financial support: Private financial suport of Gastro Obeso Center (GOC); AFIP (Associação de Fundo de Incentivo a Pesquisa).

there are already numerous studies addressing the prevalence of Obstructive Sleep Apnea in bariatric surgery candidates, the main attribute that differs this study from others is that it objectively defines anthropometric measures easily obtained during clinical evaluation, establishing a cut-off point in order to define who should be referred for polysomnography. Other studies lack this objectivity and clarity.

Therefore, the present study of obese patients eligible for MBS intervention in a private clinic aimed to (i) Assess the anthropometric measurements, along with the clinical characteristics, and quality of life profiles of these patients; (ii) Determine the occurrence and severity of OSA using polysomnography; and to (iii) Identify the best anthropometric and clinical indicators to predict OSA in obese subjects.

METHODS

To achieve the aforementioned proposed objectives, a prospective observational study was carried out from June 2015 to October 2018, using consecutive sampling of patients eligible for bariatric and metabolic surgery in a private clinic Gastro Obeso Center in the city of São Paulo, Brazil (GOB) with a diagnosis of obesity and a BMI ≥ 40, or a BMI of ≥ 35 kg/m² accompanied by comorbidities associated with obesity. The present study was approved by the Ethics and Research Committee of the Federal University of São Paulo (Universidade Federal de São Paulo), under No. 503.590, approved on: 12/20/2013, with the Certificate of Presentation for Ethical Consideration (CAAE, acronym in Portuguese) number: 18258413.4.0000.5505.

The inclusion criteria for the study were: patients diagnosed with obesity referred for metabolic and bariatric surgery, being over 18 years old, being of either sex, having a body mass index (BMI) ≥ 40, or ≥ 35 kg/m² with associated comorbidities, and agreeing to participate in the study by signing an informed consent form.

The exclusion criteria were: individuals with sleep deprivation (<4 hours/night); with psychiatric disorders that could hinder the participation in the tests; with insomnia; being diagnosed alcoholics; working in shifts; patients using neuroleptic and hypnotic drugs; having decompensated clinical diseases; individuals with learning disorders unable to complete the questionnaires; having movement disorders (neuromuscular, rheumatic or orthopedic diseases), since questionnaires concerning quality of life refer to movement skills; and patients undergoing OSA treatment.

The clinical evaluation consisted of a physical examination, which assessed the patients' anthropometric characteristics, general health status and comorbidities. A review of the patient's medical record was also carried out in order to obtain information along with a full abdominal ultrasound.

For the classification of the nutritional status, the body mass index (BMI) was calculated in kg/m² . Abdominal and hip circumference were assessed using a tape measure with the undressed patient in an upright position, measured at the level of the umbilicus and at the largest part of the hip, respectively. This data was then used to calculate the waist-to-hip ratio (WHR). Neck circumference was measured using a horizontal line at the middle point of the thyroid cartilage.[15-17]

As for the soft tissues, the palatine tonsils were measured and the modified Mallampati classification was evaluated.[18]

The Epworth Sleepiness Scale (ESS) is a subjective assessment of excessive daytime sleepiness (EDS).[19,20] The maximum score is 24 points, and patients with a score greater than or equal to 10 were considered somnolent.

The Berlin Questionnaire contains questions about sleep, snoring, the presence of respiratory pauses, daytime sleepiness, BMI as well as about systemic arterial hypertension, and the answers obtained were used to classify the patients' risk of OSA.[21-23]

The Functional Outcomes of Sleep Questionnaire (FOSQ) test measures quality of life and is designed specifically for people with sleep disorders.[24] The results allow health professionals to analyze how therapy would improve the patient's quality of life related to sleep. By completing the questionnaire periodically, the patients provided important information about the treatment effectiveness.

The Medical Outcomes Short-Form Health Survey (SF-36) is a multidimensional questionnaire comprising 36 items, in 8 scales or components: functional capacity (10 items), physical aspects (4 items), pain (2 items), general health status (5 items), vitality (4 items), social aspects (2 items), emotional aspects (3 items), mental health (5 items), as well as one question related to a comparative assessment between current and previous health conditions. It assesses both negative (disease or illness) and positive aspects of health (well-being).[25]

Full-night PSG was performed before and at least three months after the operation at the XX Institute, (XXX) using a digital polysomnography (Embla Ò N7000, Embla Systems, Inc., Broomfield, CO, USA). Surface electrodes were used to record a electroencephalography (EEG) (C3-A2, C4-A1, O2-A1, O1-A2); a chin and anterior tibialis electromyography; a bilateral electrooculogram and an electrocardiography (modified lead V1). Breathing was monitored with a nasal cannula with flow measurement using a pressure transducer along with a thermistor, and respiratory effort was assessed by inductance plethysmography of the chest and abdomen.

Pulse oximetry was used to measure oxygen saturation. Body position was evaluated by placing a sensor over the region of the sternum bone. A tracheal microphone allowed for the snoring to be recorded.

Sleep staging, respiratory events, arousals and periodic limb movements were assessed using the criteria of the American Academy of Sleep Medicine (AASM)[14], both apneas and hypopneas scores were evaluated according to the recommended protocols of the American Academy of Sleep Medicine.[14,26]

The following parameters were obtained: sleep latency in minutes; REM sleep latency in minutes; total recording time (TTR) in minutes; total sleep time (TST) in minutes; sleep efficiency; sleep stages (0, 1, 2, 3 and REM) calculated as a percentage of TST; number of microarousal and arousal index (AI) (per hour of sleep); respiratory events (apneas and hypopneas, and arousals related to respiratory effort); oxyhemoglobin saturation in percentage (baseline, average, minimum and percentage of total recording time with SpO_2 <90%); oxyhemoglobin desaturation index, REM sleep desaturation index, non-REM sleep desaturation index; where the oxygen desaturation Index (ODI) = total number of desaturations/total sleep time (min) x 60.

The sample calculation was made using the G Power software and was based on previous data from a pilot study with an effect size of f: 0.25 (F Test Manova), and p ≤0.05, as well as an observed power of 0.90 for comparison of baseline AHI score between the four groups, as described in the polysomnographic evaluation: i) without OSA ii) with mild OSA (≥5-15) iii) with moderate OSA (> 15-30) iv) with severe OSA (> 30). Thus, the sample size required was estimated to be n = 40 volunteers, with the assumption of a 20% sample loss, amounting to a required sample of n = 48 volunteers).

The statistical analysis was performed using the SPSS software (IBM, SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). To verify the normality of the continuous variables, the Kolmogorov-Smirnov test was used. The z-score was used to standardize data that did not follow the normal distribution curve.

For the characterization of the studied groups, a descriptive analysis was applied (mean ± standard deviations). For the polysomnographic variables analysis and the questionnaires, the univariate General Linear Model (GLM) was used to compare the groups. The categorical data analysis was performed using the Chi-square test and, when necessary, the Fisher's test.

The significance level adopted for the study was $\alpha \leq 0.05$. The receiver operating characteristic (ROC) curve was explored and constructed in order to establish cut-off points for anthropometric measurements as risk prediction of OSA prognosis (considering an AHI ≥ 15).

RESULTS

Sixty patients were initially selected, 46 of whom agreed to take part in the preoperative evaluation (ten did not want to undergo the medical examination, three did not meet the inclusion criteria due to the absence of comorbidities associated with a BMI bellow 40, and one was excluded due to the use of neuroleptics.

In our sample, OSA was observed in 76% of patients, 17% with mild apnea, 24% with moderate, and 35% with severe. Table 1 shows the descriptive data of the sample with the comparison of the four groups: The severe group had the highest values of waist circumference(p=0.008), WHR (p=0.03), EDS (p=0.04), highest percentage risk of apnea (p=0.009),as well as a greater association with hepatic steatosis (p=0.04) and arterial hypertension (p=0.009). The mild OSA group presented a higher prevalence of women.

Table 2 shows the comparison between the polysomnographic variables among the four groups: without OSA, and groups with OSA (mild, moderate and severe). In the evaluation of the apnea hypopnea index (AHI), as expected, there were significant differences between the groups, as this variable was the classification criterion for patient stratification (p<0.001) (Table 2).

In the evaluation of sleep stages, there was a statistical significance only in the N1 stage, with a statistical difference between the groups, the highest percentage seen in the severe OSA group, which also showed a higher rate of arousals (p<0.001). The severe OSA group also showed greater values for supine AHI, REM AHI, NREM AHI, followed by the moderate OSA group (p<0.001). In the assessment of the mean (p=0.002), the baseline (p=0.03) and the minimum SpO_2 (p=0.001), as shown in Table 2, the severe OSA group showed lower levels of saturation. In the evaluation of SpO_2 <90%, a higher percentage of desaturation was found in the severe OSA group, when compared with the other groups(p<0.001). In the assessment of the desaturation index regarding REM, non-REM and oxygen desaturation index (ODI), the severe OSA group had higher rates, followed by the moderate OSA group (p<0.001)

When exploring the total sample of obese patients with OSA (moderate-to-severe category, AHI ≥ 15), and based on a preliminary analysis of the descriptive data, the variables identified a statistical difference between groups, namely: somnolence (ESS), abdominal circumference, and WHR (see Table 1). When exploring these variables as risk factors of AHI ≥ 15, we analyzed the anthropometric variables and identified WHR as the best indicator, with an area under the curve of 0.77 (p = 0.02) with a cut-off value of 0.95. Another strong risk prediction for OSA prognostic investigated was neck circumference (AUC:0.59, p:0.30), but it was not considered a significant factor. (Figure 1). Figure 1 depicts the WHR as a predictor variable of moderate-to-severe OSA.

Figure 2 shows the comparison of WHR between the groups: "without OSA + mild" and "moderate + severe".

Table 1. Descriptive data of the sample.

Variables	Total (n = 46)	Without OSA (n = 11)	Mild OSA (n = 8)	Moderate OSA (n = 11)	Severe OSA (n = 16)	P
Age (years)	39 ± 9	32 ± 7	40 ± 10	37 ± 7	40 ± 9	0.07
Female Gender	26 (56.5%)	7 (63.6%)	8 (100%) ¤	5 (45.5%)	6 (37.5%)	**0.02** ¤
Weight (kg)	120.0 ± 2.5	115.0 ± 15.0	110.0 ± 12.8	112.0 ± 23.0	130.5 ± 22.0	0.11
Height (m)	1.6 ± 8.0	1.6 ± 9.0	1.6 ± 5.0	1.6 ± 10.0	1.7 ± 6.5	0.06
WHR	0.90 ± 0.08	0.90 ± 0.06	0.85 ± 0.09 *	0.93 ± 0.08	0.95 ± 0.08	**0.03 ***
WC (cm)	123.0 ± 13.6	117.0 ± 7.6 Δ	115.5 ± 6.0 *	118.0 ± 12.0	130.0 ± 14.0	**0.008 Δ***
CC (cm)	38.0 ± 4.0	39.0 ± 3.0	35.9 ± 3.6	38.0 ± 4.0	40.0 ± 4.0	0.11
BMI (kg/m)	42.0 ± 5.0	41.0 ± 5.0	41.0 ± 4.0	40.8 ± 5.5	43.0 ± 5.0	0.54
Modified Mallampati Classification						
Grade 2	11 (23.9%)	5 (45.4%)	3 (27.3%)	1 (9.1%)	2 (18.2%)	
Grade 3	22 (47.8%)	4 (18.2%)	5 (22.7%)	7 (31.8%)	6 (27.3%)	0.07
Grade 4	13 (28.3%)	2 (15.5%)	0 (0%)	3 (23.0%)	8 (61.5%)	
Tonsils						
Grade 1	41 (89.1%)	11 (26.8%)	7 (17.1%)	10 (24.4%)	13 (31.7%)	0.41
Grade 2	5 (10.9%)	0 (0%)	1 (20.0%)	1 (20.0%)	3 (60.0%)	
SAH						
Yes	15 (32.6%)	1 (6.7%)	0 (0%) *	5 (33.3%)	9 (60.0%)	**0.009** ¤
DM2						
Yes	4 (8.7%)	0 (0%)	0 (0%)	1 (25.0%)	3 (75.0%)	0.27
DLP						
Yes	7 (15.1%)	1 (14.3%)	2 (28.6%)	1 (14.3%)	3 (42.8%)	0.70
Hypothyroidism						
Yes	5 (10.9%)	0 (0%)	1 (20.0%)	2 (40.0%)	2 (40.0%)	0.56
Hepatic steatosis						
Yes	38 (82.6%)	6 (15.8%)	7 (18.4%)	10 (26.3%)	15 (39.5%) ¤	**0.04** ¤
Questionnaires						
ESS	13.0 ± 4.2	8.3 ± 2.3 Δ	12.0 ± 3.7	12.4 ± 5.2	14.7 ± 3.6	**0.04** Δ
Berlin						
(Risk of OSA)	32 (69.6%)	2 (6.3%)	4 (12.5%)	10 (31.2%)	16 (50.0%) ¤	**0.009** ¤
Quality of life						
SF-36 total	39.9 ± 15.5	43.0 ± 17.5	39.5 ± 19.6	32.5 ± 70	44.0 ± 15.0	0.22
Total FOSQ	14.0 ± 3.0	14.7 ± 4.0	14.3 ± 3.0	15.0 ± 2.0	14.0 ± 4.0	0.96

WC: waist circumference; CC: cervical circumference; WHR: waist-to-hip ratio; ESS: Epworth Sleepiness Score; SAH: systemic arterial hypertension; DM2: type 2 diabetes mellitus; DLP: dyslipidemia, SF36: Short-Form Health Survey; FOSQ: Functional Outcomes of Sleep Questionnaire (FOSQ); BMI: Bone Mass Index.
WHR: * mild vs severe , p = 0.02; Abdominal circumference : Δ without OSA vs severe, p = 0.03; * mild vs severe , p = 0.02 ; ESS: Δ group without OSA vs severe, p = 0.002; Gender: ¤ intra group statistical difference mild OSA: female (8) vs. male (0); Berlin: ¤ intra group statistical difference severe OSA, yes (n: 16) vs no (n: 1); Hepatic steatosis: ¤ intra group statistical difference severe OSA group, yes (n: 15) vs no (n: 1); SAH: * statistical difference between severe OSA group, yes (n: 9) vs mild OSA (n: 0).
Chi Square/Fisher test; p <0.05; Univariate GLM test.

In Table 3 indicates that, when evaluating WHR in patients with moderate-to-severe OSA (AHI> 15 events/h), 57% of subjects with AHI> 15 presented altered WHR (> 0.95) (true positive), and 19% of volunteers with mild OSA or without OSA (AHI <15) presented WHR> 0.95 (false positive).

In table 4, a PPV of WHR demonstrated that 83% of patients with WHR > 0.95 have OSA (AHI>15), with diagnostic accuracy of 66%. Table 4 shows the likelihood ratio of variables, being either a positive test (WHR > 0.95 in the sample with AHI> 15) or a negative test (WHR <0.95 in the sample with AHI> 15).

Table 2. Comparison of polysomnography between groups.

Variables	Total (n = 46)	Without OSA (n = 11)	Mild OSA (n = 8)	Moderate OSA (n = 11)	Severe OSA (n = 16)	p
Sleep efficiency	82.6 ± 10.2	83.7 ± 9.6	86.0 ± 13.3	79.4 ± 14.6	83.4 ± 3.8	0.70
TST	341.3 ± 62.2	366.7 ± 79.0	329.0 ± 64.6	318.0 ± 70.0	346.0 ± 35.4	0.29
N1	12.4 ± 11.0	11.3 ± 13.3	8.2 ± 4.9	7.6 ± 2.9 ◊	18.6 ± 13.0	**0.05** ◊
N2	51.8 ± 7.2	49.4 ± 8.9	52.5 ± 7.3	51.5 ± 4.0	53.4 ± 7.8	0.56
N3	18.6 ± 9.0	21.5 ± 9.3	21.0 ± 5.6	21.4 ± 6.6	13.5 ± 10.3	0.13
REM	17.0 ± 6.7	17.8 ± 8.6	18.2 ± 5.4	19.5 ± 5.8	14.5 ± 6.0	0.24
AI	25.7 ± 23.1	14.2 ± 15.2 Δ	12.8 ± 8.1 *	12.5 ± 5.0◊	49.2 ± 22.2	**<0.001** Δ * ◊
AHI	30.0 ± 30.5	2.2 ± 1.34 Δ #	10.0 ± 3.0 *	21.4 ± 4.4◊	65.1 ± 29.9	**<0.001** Δ * ◊ #
AHI REM	39.2 ± 26.7	7.4 ± 8.41 Δ #	22.0 ± 9.1 * •	47.7 ± 17.9	62.0 ± 19.0	**<0.001** Δ * • #
AHI NREM	30.4 ± 40.4	1.3 ± 1.0 Δ	7.6 ± 4.7 *	14.9 ± 5.2 ◊	72.4 ± 43.6	**<0.001** Δ * ◊
AHI Supine	31.3 ± 31.9	2.7 ± 1.9 Δ #	12.2 ± 11.8 *	27.7 ± 8.6◊	65.8 ± 30.0	<0.001 Δ * ◊ #
AHI Non supine	7.2 ± 11.5	2.2 ± 4.8	1.2 ± 2.1	6.8 ± 7.5	14.6 ± 16.5	0.08
Basal SpO_2	94.3 ± 2.1	95.4 ± 1.2 Δ	94.5 ± 1.5	94.9 ± 2.0	93.2 ± 2.5	**0.03** Δ
Mean SpO_2	92.2 ± 2.4	94.3 ± 0.8 Δ	92.9 ± 1.0 *	93.1 ± 1.7◊	89.8 ± 4.6	**0.002** Δ ◊ *
Min SpO_2	81.1 ± 9.8	87.9 ± 3.4 Δ	85.7 ± 3.0 *	80.0 ± 9.5	74.9 ± 11.3	**0.001** Δ *
SpO_2 <90%	12.2 ± 21.8	0.5 ± 0.8 Δ	3.8 ± 7.2 *	4.4 ± 5.0 ◊	29.9 ± 29.4	**<0.001** Δ * ◊
Desat ind REM	32.8 ± 24.0	7.0 ± 7.3 Δ #	20.6 ± 9.5 * •	42.6 ± 10.0	52.5 ± 22.4	**<0.001** Δ * • #
Desat ind NREM	21.5 ± 27.6	1.00 ± 0.99 Δ	5.6 ± 4.1 *	16.0 ± 7.2 ◊	49.9 ± 30.2	**<0.001** Δ * ◊
ODI	28.4 ± 31.0	2.1 ± 1.0 Δ	8.6 ± 3.0*	21.7 ± 8.3 ◊	61.0 ± 30.7	**<0.001** Δ * ◊

N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3; REM: rapid eye movement; AI: Arousal index; SpO_2: saturation; SpO_2 min: Minimum saturation; Desat ind: Desaturation index; ODI: oxygen desaturation index = total number of desaturations/total sleep time (min) x 60.
Statistical differences between groups: Δ Without OSA vs severe OSA; # Without OSA vs moderate; * OSA mild vs severe OSA; • moderate OSA vs mild OSA; ◇ moderate OSA vs severe OSA; N1: ◦ p = 0.05; Arousal: Δ, p <0.001; *, p <0.001; ◦ p <0.001; AHI: Δ p <0.001; * p <0.001; ◇p <0.001; # p: 0.02; Average saturation: Δ p: 0.002; ◇ p: 0.04; Basal saturation: Δ p: 0.04; Minimum saturation: Δ p: 0.002; * p: 0.02; Sat <90: Δ p: 0.001; * p: 0.01; ◇ p: 0.005; Supine AHI: Δ p <0.001; *, p <0.001; ◇ p <0.001; REM desaturation index: Δ, p <0.001; * p <0.001; • p: 0.03; NREM desat index: Δ p <0.001; * p <0.001 *; ◇ p: 0.001; ODI: Δ p <0.001; * <0.001; ◇ p <0.001; AHI REM: Δ, p <0.001; * p <0.001; • p: 0.005; AHI NREM: Δ p <0.001; * p <0.001; ◇ p <0.001.
Univariate GLM test, p <0.05 * Bonferroni *post hoc*.

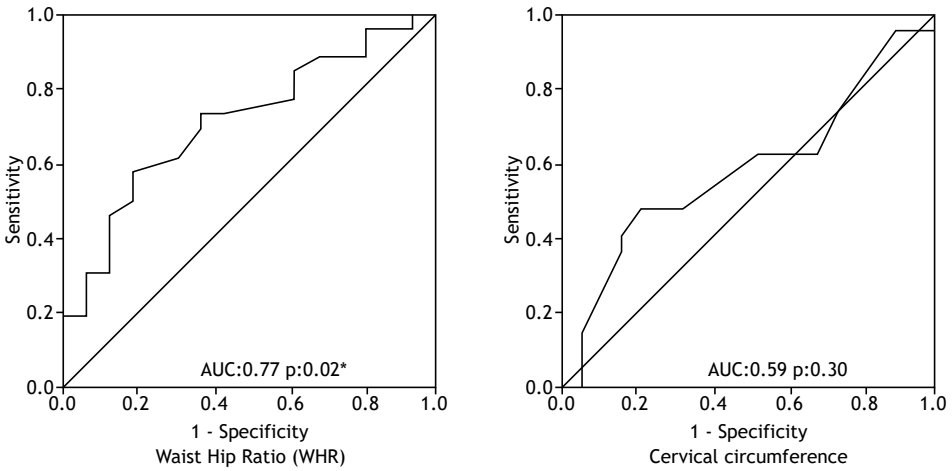

Figure 1. ROC Curve Analysis_WHR as a predictive variable of moderate and severe OSA.

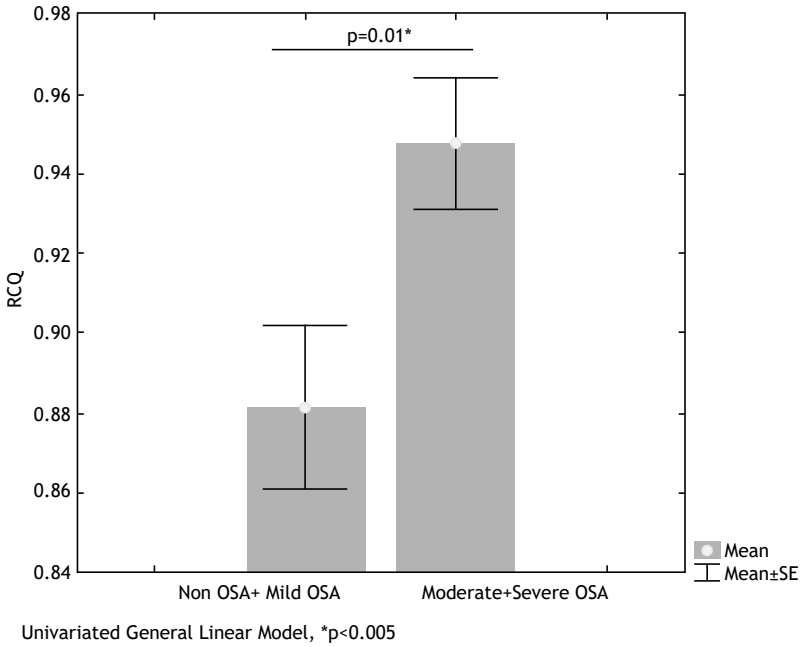

Figure 2. Comparison of WHR in patients with different severities of OSA. Univariated General Linear Model.

Table 3. Evaluation of association between WHR and moderate –to-severe OSA.

	AHI <15	AHI> 15	Total***
WHR <0.95	13 (81.3%)	11 (42.3%) **	24
WHR> 0.95	3 (18.7%) **	15 (57.7%)	18

WHR: waist-to-hip ratio. Fisher's exact test. **difference between OSA groups, p<0.01; ***4 missing - WHR.

Table 4. Likelihood ratios of positive and negative test in AHI>15 events/h samples.

Variable	Sens.	Sp.	NPP	PPV	LR (+)	LR (-)	Accuracy
WHR	57%	**81%**	54%	**83%**	3.07	0.52	66%
ESS	**88%**	76%	**90%**	72%	2.44	0.18	73%
Abdominal Circumference	33%	65%	33%	67%	0.95	1.02	54%
Neck Circumference	77%	37%	80%	33%	1.24	0.59	68%

WHR: waist-to-hip ratio; ESS: Epworth Scale Somnolence; Sens. = sensitivity; Sp. = Specificity; NPP = negative predictive value; PPV = positive predictive value; LR(+) = positive likelihood ration; LR(-) = negative likelihood ratio.

DISCUSSION

In summary, the analysis of a sample of patients referred to a private clinic for MBS intervention allowed us to conclude that there was a predominance of young morbidly obese women, with an increased daytime somnolence, higher visceral fat and waist-to-hip-ratio (WHR). Among the most frequent comorbidities found were the systemic arterial hypertension (SAH) and the hepatic steatosis. OSA was observed in 76% of patients, 59% of whom had moderate-to-severe OSA, with a predominance of men (p: 0.01). Among the variables with statistical difference between the groups, WHR was the only indicator of an AHI ≥ 15, with a cut-off value of 0.95 and accuracy of 66%, with higher positive predictive values than negative predictive values, being demonstrated as a powerful risk factor for prognostic screening of these patients, also being three times more likely to present an increase in moderate-to-severe apnea patients

The study sample profile was consistent with that described in the literature, with a greater demand from young women for surgery to treat obesity, as well as a higher occurrence of OSA among the comorbidities[27,28] A systematic review of patients eligible for bariatric surgery from the Brazilian Unified Health System (SUS) showed prevalence of patients with an average age of 41 years, an average BMI of 48.6 kg/m², with 79% being female, and 60.8% hypertensive.[29] A

meta-analysis published by Chang et al. with a total of 161.756 candidates for bariatric surgery reported the prevalence of participants with an average age of 44.6 years, 79% being female, and with a BMI of 45.6 kg/m^2. Among the studies that provided information on obesity-related comorbidities, 26% of patients had type 2 diabetes, 47% had hypertension, 28% dyslipidemia, 7% cardiovascular diseases and 25% OSA.[30] In our sample, the population profile consisted of patients with less clinical severity than the described in the literature (33% with SAH, 9% with type 2 diabetes, with insulin resistance and increased LDL observed in 57% and 72% of the sample, respectively), which can be attributed to the origin of our patients, with a more privileged socioeconomic profile and with easier access to surgical treatment. The prevalence of somnolence in our sample, evaluated using the ESS, was similar to that described in the literature.[31-33]

The occurrence of OSA found in the present study is similar to that reported in other studies.[12,13,34] Patients with moderate-to-severe OSA showed a greater somnolence, and more significant alterations from an anthropometric and clinical point of view, when compared to groups without OSA or with mild OSA, with no difference in BMI. In addition, these patients presented greater desaturation as well as a lower baseline, mean and minimum saturation values. On the other hand, when comparing the anthropometric, clinical, somnolence, quality of life and polysomnographic variables in the groups of individuals without apnea with those with mild apnea, we did not find any statistically significant difference between them.

All of this corroborates the growing evidence that mild OSA is not a significant independent risk factor for cardiovascular and metabolic comorbidities, including endothelial dysfunction, reduced baroreflex sensitivity, systemic inflammation, as well as systemic arterial hypertension and insulin resistance.[35-38] In moderate-to-severe OSA, several studies have indicated an association with cardiovascular morbidity and its complications.[35-38] It is worth mentioning that it is a well-known fact that intermittent hypoxia plays a fundamental role in the development of cardiovascular variability in OSA, propagating the production of reactive oxygen species, resulting in oxidative stress and inflammation.[39]

The findings of our study show the greater effects of moderate-to-severe OSA in patients, since this data reflects visceral adiposity, and its full potential for associated complications.

Obesity alone is a risk factor for OSA. Large epidemiological studies have reported a dose-response relationship linking the prevalence of OSA with an increased BMI, neck and abdominal circumference.[15-17] Some variables have been used previously in clinical practice, but there is no standardized measurement in the literature for a predictive model regarding OSA, with neck and abdominal circumference, and waist-to-hip ratio (WHR) being the most used, as they are easy to obtain and demonstrate greater accuracy than other measures such as BMI, which does not include the fat distribution patterns.[3,16,17,40]

In this study, the most important finding was that WHR was the best indicator for identifying patients with moderate–to-severe OSA, with a sensitivity of 57% and specificity of 81%. As indicated in Tables 3 and 4, 57% of subjects with an AHI> 15 have a WHR> 0.95 (true positive) and 19% with an AHI <15 have a WHR> 0.95 (false positive). Thus, we found that WHR was three times more likely to be increased (> 0.95) in the sample with AHI> 15. This finding is of paramount clinical importance, since it can be used to screen patients with moderate-to-severe OSA with associated greater cardiovascular risk and consequently a higher surgical risk.

Additionally, the prevalence of OSA in the bariatric surgery population is higher than in the general population, and although polysomnography remains the gold standard for diagnosing these patients, it is not always easily accessible for everyone, requiring time to schedule, even in large urban centers. Therefore, the WHR measurement in our study was useful as a surrogate of moderate-to-severe OSA and, coupled with other clinical criteria, it could be used in preferential referral for polysomnography and the identification of patients with a greater severity of OSA.

Despite the small sample size, when compared to some studies described in the literature, our study included a broad assessment of all polysomnographic parameters, not only those related to respiratory events during sleep. Another limitation of our study was the lack of imaging methods for evaluation of the upper airway that might better explain individual patient differences, that being said, a visual analysis of the airway was performed and did not identify any changes among the groups.

This study allowed us to conclude that OSA was observed in 76% of patients, with 59% having moderate-to-severe apnea. In addition, the best indicator of moderate-to-severe OSA was WHR, with a cut-off value of 0.95, being three times more likely to show an increase in this group of patients.

CONFLICT OF INTEREST

The authors declare that there were no conflicts of interest in this study.

AUTHOR CONTRIBUTIONS

AFH: administration of this study, supervision, writer, investigator. LMN: supervision. DSV and RS: investigators. TDG: acquisition of financing/ resources. SMGT and LRB: supervision, writer. LEN: supervision, writer, investigator.

REFERENCES

1. WHO: World Health Organization. Obesity and Overweight: Global Strategy On Diet, Physical Activity And Health, Geneva: WHO; 2003.
2. Brasil. Ministério da Saúde. Vigitel Brasil 2016. Vigilância de Fatores de Risco e Proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde.
3. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. J Appl Physiol. 2005;99(4):1592-9. http://dx.doi.org/10.1152/japplphysiol.00587.2005. PMid:16160020.
4. Castaneda A, Jauregui-Maldonado E, Ratnani I, Varon J, Surani S. Correlation between metabolic syndrome and sleep apnea. World J Diabetes. 2018;9(4):66-71. http://dx.doi.org/10.4239/wjd.v9.i4.66. PMid:29765510.
5. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, et al. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. BMC Pulm Med. 2015;15(1):105. http://dx.doi.org/10.1186/s12890-015-0102-3. PMid:26391008.
6. Joosten SA, Hamilton GS, Naughton MT. Impact of weight loss management in OSA. Chest. 2017;152(1):194-203. http://dx.doi.org/10.1016/j.chest.2017.01.027. PMid:28185772.
7. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. Lancet Respir Med. 2013;1(1):61-72. http://dx.doi.org/10.1016/S2213-2600(12)70051-6. PMid:24321805.
8. Hamilton GS, Naughton MT. Impact of obstructive sleep apnoea on diabetes and cardiovascular disease. Med J Aust. 2013;199(8):S27-30. http://dx.doi.org/10.5694/mja13.10579. PMid:24138362.
9. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the sao paulo epidemiologic sleep study. Sleep Med. 2010;11(5):441-6. http://dx.doi.org/10.1016/j.sleep.2009.10.005. PMid:20362502.
10. Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, et al. American Association of Clinical Endocrinologist, The Obesity Society and American Society of Metabolic and Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic and nonsurgical support of the bariatric surgery patient. Endocr Pract. 2008;14(Suppl 1):1-83. http://dx.doi.org/10.4158/EP.14.S1.1. PMid:18723418.
11. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230-5. http://dx.doi.org/10.1056/NEJM199304293281704. PMid:8464434.
12. Fritscher LG, Mottin CC, Canani S, Chatkin JM. Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. Obes Surg. 2007;17(1):95-9. http://dx.doi.org/10.1007/s11695-007-9012-7. PMid:17355775.
13. Dixon JB, Schachter LM, O'Brien AE. Predicting sleep apnea and excessive day sleepiness in the severely obese– indicators for polysomnography. Chest. 2003;123(4):1134-41. http://dx.doi.org/10.1378/chest.123.4.1134. PMid:12684304.
14. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF. The AAM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
15. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284(23):3015-21. http://dx.doi.org/10.1001/jama.284.23.3015. PMid:11122588.
16. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med. 2005;165(20):2408-13. http://dx.doi.org/10.1001/archinte.165.20.2408. PMid:16287771.
17. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disorderedbreathing. JAMA. 2003;289(17):2230-7. http://dx.doi.org/10.1001/jama.289.17.2230. PMid:12734134.
18. Zonato AI, Bittencourt LR, Martinho FL, Santos JF Jr, Gregorio LC, Tufik S. Association of systematic head and neck physical examination with severity of obstructive sleep apnea-hypopnea syndrome. Laryngoscope. 2003;113(6):973-80. http://dx.doi.org/10.1097/00005537-200306000-00011. PMid:12782807.
19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. http://dx.doi.org/10.1093/sleep/14.6.540. PMid:1798888.
20. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol. 2009;35(9):877-83. http://dx.doi.org/10.1590/S1806-37132009000900009. PMid:19820814.
21. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485-91. http://dx.doi.org/10.7326/0003-4819-131-7-199910050-00002. PMid:10507956.
22. Vaz AP, Drummond M, Mota PC, Severo M, Almeida J, Winck JC. Translation of Berlin Questionnaire to Portuguese language and its application in OSA identification in a sleep disordered breathing clinic. Rev Port Pneumol. 2011;17(2):59-65. http://dx.doi.org/10.1016/S0873-2159(11)70015-0. PMid:21477567.
23. Andrechuk CRS, Netzer N, Zancanella E, Almeida AR, Ceolim MF. Cultural adaptation and evaluation of the measurement properties of the Berlin Questionnaire for Brazil. Sleep Med. 2019;60:182-7. http://dx.doi.org/10.1016/j.sleep.2019.03.022. PMid:31213394.
24. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997;20(10):835-43. PMid:9415942.
25. Ciconelli RM, Ferraz MB, Santos WS, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol. 1999;39(3):43-50.
26. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619. http://dx.doi.org/10.5664/jcsm.2172. PMid:23066376.
27. da Silva PT, Patias LD, Alvarez GC, Kirsten VR, Colpo E, de Moraes CM. Profile of patients who seek the bariatric surgery. Arq Bras Cir Dig. 2015;28(4):270-3. http://dx.doi.org/10.1590/s0102-6720201500040013. PMid:26734799.
28. Porto MCV, Brito IC, Calfa ADF, Amoras M, Villela NB, Araújo LMB. Perfil do obeso classe III do ambulatório de obesidade de um hospital universitário de salvador, Bahia. Arq Bras Endocrinol Metabol. 2002;46(6):6. http://dx.doi.org/10.1590/S0004-27302002000600011.
29. Kelles SMB, Diniz MF, Machado CJ, Barreto SM. Perfil de pacientes submetidos à cirurgia bariátrica, assistidos pelo Sistema Único de Saúde do Brasil: revisão sistemática. Cad Saude Publica. 2015;31(8):1587-601. http://dx.doi.org/10.1590/0102-311X00022714. PMid:26375639.
30. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic reviewand meta-analysis, 2003-2012. JAMA Surg. 2014;149(3):275-87. http://dx.doi.org/10.1001/jamasurg.2013.3654. PMid:24352617.
31. Perez EA, Oliveira LVF, Freitas WR Jr, Malheiros CA, Ilias EJ, Silva AS, et al. Prevalence and severity of syndrome Z in women with metabolic syndrome on waiting list for bariatric surgery: a cross-sectional study. Diabetol Metab Syndr. 2017;9:72. https://doi.org/10.1186/s13098-017-0269-2.
32. Sharkey KM, Orff HJ, Tosi C, Harrington D, Roye GD, Millman RP. Subjective sleepiness and daytime functioning in bariatric patients with obstructive sleep apnea. Sleep Breath. 2013;17(1):267-74. http://dx.doi.org/10.1007/s11325-012-0685-3. PMid:22528950.
33. Serafini FM, MacDowell Anderson W, Rosemurgy AS, Strait T, Murr MM. Clinical predictors of sleep apnea in patients undergoing bariatricsurgery. Obes Surg. 2001;11(1):28-31. http://dx.doi.org/10.1381/096089201321454079. PMid:11361164.
34. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders. inpatients evaluated for bariatric surgery. Obes Surg. 2003;13(5):676-83. http://dx.doi.org/10.1381/096089203322509228. PMid:14627460.
35. McNicholas WT. Obstructive sleep apnoea of mild severity: should it betreated? Curr Opin Pulm Med. 2017;23(6):506-11. http://dx.doi.org/10.1097/MCP.0000000000000420. PMid:28858969.
36. McNicholas WT, Bonsignore MR, Lévy P, Ryan S. Mild obstructive sleep apnoea: clinical relevance and approaches to management. Lancet Respir Med. 2016;4(10):826-34. http://dx.doi.org/10.1016/S2213-2600(16)30146-1. PMid:27245915.
37. Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a metaanalysis of prospective cohort studies. Int J Cardiol. 2013;169(3):207-14. http://dx.doi.org/10.1016/j.ijcard.2013.08.088. PMid:24161531.
38. Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. J Clin Sleep Med. 2014;10(4):355-62. http://dx.doi.org/10.5664/jcsm.3600. PMid:24733978.

39. Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. Eur Respir J. 2009;33(6):1467-84. http://dx.doi.org/10.1183/09031936.00086608. PMid:19483049.

40. Davidson TM, Patel MR. Waist circumference and sleepdisordered breathing. Laryngoscope. 2008;118(2):339-47. http://dx.doi.org/10.1097/MLG.0b013e3181587d7c. PMid:18091340.

J Bras Pneumol. 2022;48(6):e20220145
https://dx.doi.org/10.36416/1806-3756/e20220145

ORIGINAL ARTICLE

Assessment of risk factors in patients with rheumatoid arthritis-associated interstitial lung disease

Carolina Rossetti Severo[1], Carolina Chomiski[1], Marina Borba do Valle[1], Dante Luiz Escuissato[1], Eduardo dos Santos Paiva[1], Karin Mueller Storrer[1]

1. Universidade Federal do Paraná, Curitiba (PR), Brasil.

Submitted: 08 May 2022.
Accepted: 21 August 2022.

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

ABSTRACT

Objective: To assess the risk factors for interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) and to evaluate the association of ILD with the use of methotrexate as well as with joint disease activity. **Methods:** A retrospective, cross-sectional study conducted between March and December 2019 at a tertiary healthcare center, in a follow-up of RA patients who had undergone pulmonary function tests (PFT) and chest computed tomography. We evaluated the tomographic characteristics, such as the presence of ILD and its extension, as well as joint disease activity. Functional measurements, such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), were also assessed. After this, a multivariate logistic regression analysis was applied in order to identify risk factors associated with ILD. **Results:** We evaluated 1.233 patients, of which 134 were eligible for this study. The majority were female (89.6%), with a mean age of 61 years old and with a positive rheumatoid factor (86.2%). RA-associated ILD (RA-ILD) was detected in 49 patients (36.6%). We found an association of RA-ILD with age ≥= 62 year, male sex, smoking history and fine crackles in lung auscultation and a decreased DLCO. The indicators of being aged ≥ 62 years old and having moderate or high RA disease activity were both independent factors associated with RA-ILD, with an odds ratio of 4.36 and 3.03, respectively. The use of methotrexate was not associated with a higher prevalence of ILD. **Conclusion:** Age and RA disease activity are important risk factors associated with RA-ILD. Methotrexate was not associated with the development of RA-ILD in the present study.

Keywords: Rheumatoid arthritis; Interstitial lung disease; Rheumatoid arthritis- associated interstitial lung disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease with a prevalence rate ranging from 0.3 to 1% of the population, with a higher incidence in women aged between 30 and 50 years old.[1]

Although join manifestations are more prevalent, extra-articular manifestations of RA may occur in about 40% of patients, usually presenting with rheumatoid nodules, secondary Sjögren's syndrome and lung disease.[2]

The association of lung disease with RA was first described in 1948.[3] Since then, a wide range of pulmonary involvement due to this illness have been well described, such as pleurisy/pleural effusion, rheumatoid nodules, Caplan syndrome, pulmonary hypertension, bronchiolitis, bronchiectasis and interstitial lung disease (ILD).[4,5]

ILD is an important form of RA-related lung disease.[5,6] In studies with chest computed tomography (CT), its prevalence ranges from 28 to 58%,[6-8] but only 5 to 10% are estimated to be clinically relevant cases.[9,10]

This study aims to evaluate risk factors for ILD in RA patients in follow-up at an outpatient clinic of a tertiary healthcare service, as well as to assess the association of ILD with the use of methotrexate and joint disease activity.

METHODS

This was a retrospective, cross-sectional study that included patients aged ≥ 18 years old, in follow-up for RA at an outpatient clinic of a tertiary healthcare service in Brazil, from March to December 2019, who had undergone pulmonary function tests (PFTs) and chest CTs for any reason.

Patients with overlapping collagen diseases, undergoing radiation therapy with potential for radiation-induced lung injury or lung resection procedures, were excluded.

All patients were diagnosed with RA by a rheumatologist, according to specific diagnostic criteria.[11,12]

Joint disease activity data was collected from the patient's medical records and used as the last measure before

Correspondence to:
Carolina Rossetti Severo. Hospital de Clínicas, Universidade Federal do Paraná, Rua General Carneiro, 181, CEP 80060-150, Curitiba, PR, Brasil.
Tel.: +55 41 99105-1832. E-mail: carolina_severo@hotmail.com
Financial support: None.

ISSN 1806-3756

the CT scan. The following validated instruments were used: the Disease Activity Score-28 for RA (DAS-28) with C-reactive protein (DAS28-CRP), the DAS-28 with erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI). For the analysis, we stratified the patients into two groups: moderate/high and low activity/remission. We chose this stratification system on the grounds that low activity of joint disease or remission are recommended as treatment targets in clinical practice.[13,14]

Respiratory symptoms such as cough, sputum and degree of dyspnea (modified Medical Research Council (mMRC) scale), as well as data from physical examination (clubbing, fine crackles, peripheral oxygen saturation at rest), use of drugs for current RA treatment, previous use of methotrexate at any time (duration in years and maximum dose used), dosing of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), were evaluated.

The CT images were assessed independently, in random order, by two chest radiologists. Upon divergence in the interpretation of results, a final decision was reached by consensus of both radiologists. Interobserver agreement between radiologists was not calculated. The HRCT findings were categorized as absent, limited or extensive ILD, according to the extent of the involvement in five levels and classification algorithm proposed by Goh et al.[15] CT scans with more than 20% involvement were categorized as extensive ILD. CT scans presenting any abnormality less than 20% involvement were categorized as limited ILD.

Pulmonary function tests (PFTs), such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV), RV/TLC ratio, diffusing capacity for carbon monoxide (DLCO), and lung diffusion capacity corrected for alveolar ventilation (DLCO/AV) were also evaluated.

This study was approved by the Human Research Ethics Committee of the institution.

Statistical analysis

Data analysis was performed with the Excel® and SPSS Statistics v. 22.0 software.

The quantitative variable's results were described in mean and standard deviation. Categorical variables were described in frequency and percentage. The ROC curve was adjusted to evaluate the existence of cut-off points for age related to ILD (yes or no) (^{3}62 years, p = 0.013, specificity 56.3% and sensitivity 69.7%). For the comparison of the three assessments of the disease extent (absent, limited or extensive) with the quantitative variables, nonparametric Kruskal-Wallis test and post-hoc Dunn test were applied. Comparisons of disease extent assessment (limited or extensive) were made with the Mann-Whitney nonparametric test. As for the categorical variables, the comparison was made with the chi-square test. A multivariate model was adjusted to include sex, fine crackles, age and DLCO as explanatory variables (those presenting with $p < 0.05$ in the univariate analysis), in order to evaluate the control of the joint disease activity, the variables were found to be both statistically significant ($p < 0.05$) and clinically relevant.

Logistic regression models were adjusted for univariate and multivariate analysis of factors associated with ILD. The Wald test was used to assess the statistical significance of the variables and the estimated measure of association was calculated by a odds ratio with 95% confidence intervals. P-values < 0.05 indicated statistical significance.

RESULTS

Among the 1.233 patients treated from March to December 2019, 1.052 were not eligible for this study on account of insufficient data from chest CTs and/or PFTs, lack of RA diagnosis, conflicting or unavailable data (Figure 1). Other 47 patients were excluded from the study due to the following exclusion criteria: presence of another lung disease, presence of overlapping collagen disease, history of radiation therapy with potential for radiation-induced lung injury, or history of lung resection. Thus, 134 patients were included in the present study.

The participants were predominantly female (89.6%), with a mean age of 61 years old. Most patients had no smoking history (53%) and, among smokers, the mean smoking load was 22.8 packs-year. The majority of patients had positive RF (86.2%), while only 18 participants had the anti-CCP result (anti-CCP is not an easily available exam in our public health system) (Table 1).

Almost all patients had a history of prior use of methotrexate or were currently using it at the time of the analysis (93.2%).

Regarding the joint activity scales (DAS28-CRP, DAS28-ESR or CDAI), patients were stratified according to different disease activity levels, displaying discrepancies in these assessment instruments. However, more than 50% of the sample was categorized as in remission or with low activity, regardless of analyzed scale. Furthermore, CDAI was the most used disease activity score in our study, therefore, we used this tool to stratify patients presenting moderate/high disease activity for the univariate analysis.

RA-ILD was present in 49 patients (36.6%), 24.6% were considered as having limited extension disease and 11.9% as having extensive disease. Comparing patients with ILD (RA-ILD) and without ILD, age >= 62 years, smoking history and presence of fine crackles were significantly more prevalent indicators in the RA-ILD group. Although most of the patients had a preserved PFT, DLCO values were remarkably higher among those without ILD (Table 2).

The age of 62 years was used because it was the cut-off point with statistical significance indicated by the ROC curve analysis (p = 0.013) and had 69.7% of

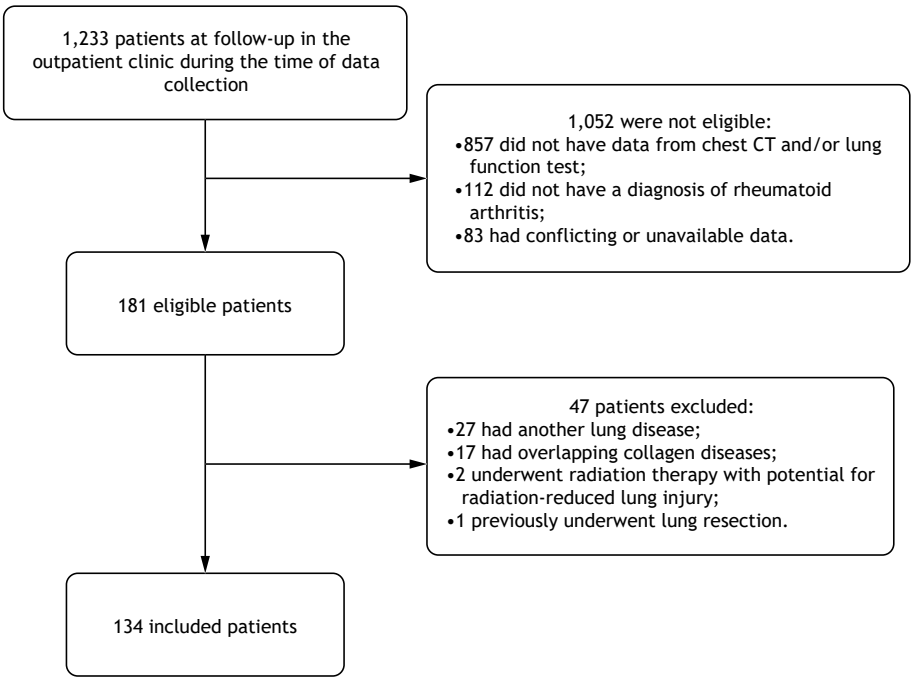

Figure 1. Study design.

sensitivity. The multivariate analysis demonstrated that being aged ≥ 62 years old and presenting moderate/high disease activity (in any of the scores) were independent factors for RA-ILD with an odds ratio of 4.36 and 3.03, respectively (Table 3).

Regarding patients treated with methotrexate (n = 124), there was no association of previous methotrexate treatment and the presence of ILD (p = 0.219). However, when ILD extension was evaluated, 9.7% presented extensive tomographic disease, while 65.3% presented absence of ILD when in use of methotrexate (p = 0.008) (Table 4).

DISCUSSION

The present study indicates that being age ≥ 62 years old, male sex, having a smoking history, and presenting fine crackles are risk factors associated with RA-ILD (presented in 36.6% of the sample). Higher DLCO values are inversely associated with RA-ILD.

The evaluation of risk factors is extremely important for RA-ILD, not only because of its relevant prevalence, but also due to the impact of the diagnosis on both treatment options and mortality.[9,10,16] Although RA is more common among females, being male is considered a risk factor for RA-ILD. This association was found in this study and had already been demonstrated by other authors.[10,16,17]

The presence of RA-related autoantibodies, especially in high titers, has been suggested to be a risk factor for RA-ILD.[2,10,17-19] Kelly et al. demonstrated that high titers of anti-CCP are strongly associated with RA-ILD.[10] In our study, it was found no positive association between positive RF or anti-CCP and RA-ILD; nevertheless, different methods were used for dosing RF, which may have contributed to creating a bias. Moreover, only a small number of patients were tested for anti-CCP, and this could also have influenced the results found herein. That being said, a recently published meta-analysis showed that patients with positive RF or anti-CCP have a higher risk of developing RA-ILD, but the analysis of subgroups by region indicated that even though patients from Asia, Africa and Europe with positive anti-CCP presented a higher risk of ILD-RA, it was not statistically significant for the American population, with two studies from the United States and one study from Mexico included in that analysis.[19] This allows questioning whether the American population has a different pattern.

Although the presence of respiratory symptoms did not present a statistical significance associated with ILD in the studied sample, one third of patients who did not present respiratory symptoms manifested ILD on the chest CT scan. A Spanish cohort study had a similar result, since 33.7% of 90 patients with RA-ILD were asymptomatic.[18] This suggests that the presence of symptoms should not be used alone, isolated Hto determine the presence of ILD in RA patients.

Fine crackles in lung auscultation were associated with the diagnosis of RA-ILD, demonstrating that a

Table 1. Baseline population characteristics.

Clinical-epidemiological characteristics [n = 134]	
Female sex, n (%)	120 (89.6)
Age in years, mean ± standard deviation	61 ± 11
Current or previous smoking history, n (%) [n = 132]	62 (47)
Illness duration in years, mean ± standard deviation	13 ± 9
Positive rheumatoid factor, n (%) [n = 130]	112 (86.2)
Presence of respiratory symptoms, n (%) [n = 133]	106 (79.7)
Joint disease activity DAS28-CRP [n = 105]	
Remission, n (%)	51 (48.6)
Low activity, n (%)	16 (15.2)
Moderate activity, n (%)	31 (29.5)
High activity, n (%)	7 (6.7)
Joint disease activity DAS28-ESR [n = 99]	
Remission, n (%)	28 (28.3)
Low activity, n (%)	22 (22.2)
Moderate activity, n (%)	36 (36.4)
High activity, n (%)	13 (13.1)
Joint disease activity CDAI [n = 115]	
Remission, n (%)	12 (10.4)
Low activity, n (%)	53 (46.1)
Moderate activity, n (%)	34 (29.6)
High activity, n (%)	16 (13.9)
Lung functional characteristics [n = 134]	
Absolute FVC, mean ± standard deviation	2.99 ± 0.99
Relative FVC, mean ± standard deviation	98.2 ± 22
Absolute DLCO, mean ± standard deviation [n = 121]	19.9 ± 5.34
Relative DLCO, mean ± standard deviation [n = 121]	96.4 ± 27.9
Tomographic extension [n = 134]	
Absent, n (%)	85 (63.4)
Limited, n (%)	33 (24.6)
Extensive, n (%)	16 (11.9)

CDAI: Clinical Disease Activity Index; FVC: Forced vital capacity; DAS28-CRP: Disease Activity Score-28 for RA (DAS-28) with C-reactive protein; DAS28-ESR: Disease Activity Score-28 for RA (DAS-28) with erythrocyte sedimentation rate; DLCO: Diffusing capacity for carbon monoxide.

Table 2. Characteristics of patients with rheumatoid arthritis (RA) stratified by presence and absence of interstitial lung disease (ILD).

	N=134	RA-ILD absent	RA-ILD present	p
Age ≥ 62 years old	67	32 (47.8%)	35 (52.2%)	<0.001
Male sex	14	4 (28.6%)	10 (71.4%)	0.008
Previous smoking history	45	22 (48.9%)	23 (51.1%)	0.024
Presence of respiratory symptoms	106	67 (63.2%)	39 (36.8%)	0.738
Presence of fine crackles	26	9 (34.6%)	17 (65.4%)	0.001
Previous treatment with methotrexate	124	81 (65.3%)	43 (34.7%)	0.219
Moderate/high disease activity	50	29 (58%)	21 (42%)	0.075
Positive rheumatoid factor	112	68 (60.7%)	44 (39.3%)	0.172
FVC (%) mean ± standard deviation	134	100.8 ± 19.6	93.7 ± 25.2	0.073
DLCO (%) mean ± standard deviation	121	101.5 ± 26.6	87.6 ± 28.2	0.010

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide; RA-ILD: Rheumatoid arthritis-associated interstitial lung disease.

careful lung auscultation should be performed in all RA patients, regardless of their complaints related to their respiratory symptoms. It is a low-cost examination with no contraindications that can contribute to an early diagnosis. A prospective blind study with a sample of 148 patients showed a correlation between bilateral fine

Table 3. Multivariate analysis.

	p	OR	CI95 %
Age ≥ 62 years old	0.005	4.36	1.57 - 12.09
Male sex	0.215	3.29	0.50 - 21.7
Presence of fine crackles	0.774	1.22	0.32 - 4.58
Absolute DLCO	0.235	0.94	0.86 - 1.04
Moderate/high disease activity	0.027	3.03	1.14 - 8.09

DLCO: Diffusing capacity for carbon monoxide.

Table 4. Association of previous treatment with methotrexate with tomographic extension of interstitial lung disease.

		Tomographic extension			p
		Absent	Limited	Extensive	
Previous treatment with methotrexate	No	4 (44.4%)	1 (11.1%)	4 (44.4%)	0.008
	Yes	81 (65.3%)	31 (25%)	12 (9.7%)	

crackles and the presence of fibrotic ILD. This type of abnormality in auscultation was the predictive factor most related to usual interstitial pneumonia (UIP) pattern in chest –CT scans, which is the most frequent tomographic pattern observed in RA-ILD patients.[20] Studies using digital stethoscopes and sound analysis of velcro crackles showed that this new technology has better accuracy if compared with traditional auscultation, presenting a 84 to 90% against a 60 to 70% precision, respectively.[21,22]

In the multivariate analysis, moderate or high joint disease activity were considered independent factors associated with RA-ILD, with an odds ratio of 3.03. This suggests the importance of controlling systemic inflammation for the prevention of RA-ILD development. This was already suggested in a prospective cohort study with 1.419 patients which showed that joint activity in RA is associated with a higher risk of developing ILD.[23] Other studies demonstrate that the CDAI score is also associated with ILD activity.[24,25]

In our study, the mean DLCO was found to be normal in the RA-ILD group, however, it was significantly lower than the group without RA-ILD. Despite the fact that several cut-off points have already been proposed in the literature to facilitate ILD screening, there is no consensus,[21,26,27] and even with a low DLCO cut-off point of 47%, accuracy and sensitivity were low (54.9% and 30.8%, respectively).[21]

The vast majority of patients in the present study were treated with methotrexate at some point; it is noteworthy that 65.3% of these patients were not diagnosed with RA-ILD, and extensive ILD was only present in 9.7% of cases, suggesting a protective factor. Although methotrexate has been historically considered a causal factor of ILD, recent evidence corroborate the findings of our study.[17,28-30]

The results herein should be interpreted considering some limitations. The retrospective nature of the research design is a major limitation of our study. In addition, the study was conducted in a single center. Also, for being a public healthcare profile, some data were incomplete, such as anti-CCP. However, most of the data found is consistent with the literature, a fact that supports this study's relevance.

In conclusion, age and RA disease activity were found to be important risk factors associated with RA-ILD. Methotrexate use was not associated with the development of RA-ILD in the present study.

AUTHOR CONTRIBUTIONS

CRS: investigation, data curation, formal analysis, visualization and writing of the original draft. CC: investigation and formal analysis. MBV: investigation and data curation. DLE and ESP: investigation, formal analysis and writing of the reviewed manuscript. KMS: conceptualization, investigation, formal analysis, visualization and writing of the reviewed manuscript. All authors contributed to the final version of the manuscript.

REFERENCES

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and Prevalence of Rheumatoid Arthritis, Based on the 1987 American College of Rheumatology Criteria: a systematic review. Semin Arthritis Rheum. 2006;36(3):182-8. http://dx.doi.org/10.1016/j.semarthrit.2006.08.006. PMid:17045630.
2. Turesson C, O'Fallon WM, Crowson CS, Gabriel ES, Matteson ES. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003;62(8):722-7. http://dx.doi.org/10.1136/ard.62.8.722. PMid:12860726.

3. Ellman P, Ball RE. Rheumatoid disease with joint and pulmonary manifestations. BMJ. 1948;2(4583):816-20. http://dx.doi.org/10.1136/bmj.2.4583.816. PMid:18890308.
4. Remy-Jardin M, Remy J, Cortet B, Mauri F, Delcambre B. Lung changes in rheumatoid arthritis: CT findings. Radiology. 1994;193(2):375-82. http://dx.doi.org/10.1148/radiology.193.2.7972746. PMid:7972746.
5. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med. 1998;19(4):667-85, viii. http://dx.doi.org/10.1016/S0272-5231(05)70109-X. PMid:9917959.
6. Huang S, Kronzer VL, Dellaripa PF, Deane KD, Bolster MB, Nagaraja V, et al. Rheumatoid arthritis–associated interstitial lung disease: current update on prevalence, risk factors, and pharmacologic treatment. Curr Treatm Opt Rheumatol. 2020;6(4):337-53. http://dx.doi.org/10.1007/s40674-020-00160-z. PMid:33282632.
7. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med. 1997;156(2 Pt 1):528-35. http://dx.doi.org/10.1164/ajrccm.156.2.9609016. PMID: 9279235.
8. Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2017;36(4):817-23. http://dx.doi.org/10.1007/s10067-017-3561-5. PMid:28191607.
9. Habib HM, Eisa AA, Arafat WR, Marie MA. Pulmonary involvement in early rheumatoid arthritis patients. Clin Rheumatol. 2011;30(2):217-21. http://dx.doi.org/10.1007/s10067-010-1492-5. PMid:20503061.
10. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study. Rheumatology (Oxford). 2014;53(9):1676-82. http://dx.doi.org/10.1093/rheumatology/keu165. PMid:24758887.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81. http://dx.doi.org/10.1002/art.27584. PMid:20872595.
12. England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). 2019;71(12):1540-55. http://dx.doi.org/10.1002/acr.24042. PMid:31709779.
13. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26. http://dx.doi.org/10.1002/art.39480. PMid:26545940.
14. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15. http://dx.doi.org/10.1136/annrheumdis-2015-207524. PMid:25969430.
15. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis. Am J Respir Crit Care Med. 2008;177(11):1248-54. http://dx.doi.org/10.1164/rccm.200706-877OC. PMid:18369202.
16. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis - A population-based study. Arthritis Rheum. 2010;62(6):1583-91. http://dx.doi.org/10.1002/art.27405. PMid:20155830.
17. Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ Open. 2019;9(5):e028466. http://dx.doi.org/10.1136/bmjopen-2018-028466. PMid:31061059.</jrn>0
18. Bonilla Hernán MG, Gómez-Carrera L, Fernández-Velilla Peña M, Álvarez-Sala Walther R, Balsa A. Prevalence and clinical characteristics of symptomatic diffuse interstitial lung disease in rheumatoid arthritis in a Spanish population. Rev Clin Esp (Barc). 2022;222(5):281-7. http://dx.doi.org/10.1016/j.rceng.2021.01.011. PMid:34583914.
19. Xie S, Li S, Chen B, Zhu Q, Xu L, Li F. Serum anti-citrullinated protein antibodies and rheumatoid factor increase the risk of rheumatoid arthritis–related interstitial lung disease: a meta-analysis. Clin Rheumatol. 2021;40(11):4533-43. http://dx.doi.org/10.1007/s10067-021-05808-2. PMid:34189672.
20. Sgalla G, Walsh SLF, Sverzellati N, Fletcher S, Cerri S, Dimitrov B, et al. "Velcro-type" crackles predict specific radiologic features of fibrotic interstitial lung disease. BMC Pulm Med. 2018;18(1):103. http://dx.doi.org/10.1186/s12890-018-0670-0. PMid:29914454.
21. Manfredi A, Cassone G, Cerri S, Venerito V, Fedele AL, Trevisani M, et al. Diagnostic accuracy of a velcro sound detector (VECTOR) for interstitial lung disease in rheumatoid arthritis patients: the InSPIRAtE validation study (INterStitial pneumonia in rheumatoid ArThritis with an electronic device). BMC Pulm Med. 2019;19(1):111. http://dx.doi.org/10.1186/s12890-019-0875-x. PMid:31221137.
22. Pancaldi F, Sebastiani M, Cassone G, Luppi F, Cerri S, Della Casa G, et al. Analysis of pulmonary sounds for the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis. Comput Biol Med. 2018;96:91-7. http://dx.doi.org/10.1016/j.compbiomed.2018.03.006. PMid:29550468.
23. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid Arthritis Disease Activity Predicting Incident Clinically Apparent Rheumatoid Arthritis–Associated Interstitial Lung Disease: A Prospective Cohort Study. Arthritis Rheumatol. 2019;71(9):1472-82. http://dx.doi.org/10.1002/art.40904. PMid:30951251.
24. Rojas-Serrano J, Mejía M, Rivera-Matias P, Herrera-Bringas D, Pérez-Román D, Pérez-Dorame R, et al. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): a possible association between disease activity and prognosis. Clin Rheumatol. 2022;41(6):1741-7. http://dx.doi.org/10.1007/s10067-021-06040-8. PMid:35112192.
25. Pérez-Dórame R, Mejía M, Mateos-Toledo H, Rojas-Serrano J. Rheumatoid arthritis-associated interstitial lung disease: lung inflammation evaluated with high resolution computed tomography scan is correlated to rheumatoid arthritis disease activity. Reumatol Clin. 2015;11(1):12-6. http://dx.doi.org/10.1016/j.reuma.2014.02.007. PMid:24913966.
26. Wang T, Zheng XJ, Liang BM, Liang ZA. Clinical features of rheumatoid arthritis-associated interstitial lung disease. Sci Rep. 2015;5(1):14897. http://dx.doi.org/10.1038/srep14897. PMid:26443305.
27. Yilmazer B, Gümüştaş S, Coşan F, İnan N, Ensaroğlu F, Erbağ G, et al. High-resolution computed tomography and rheumatoid arthritis: semi-quantitative evaluation of lung damage and its correlation with clinical and functional abnormalities. Radiol Med (Torino). 2016;121(3):181-9. http://dx.doi.org/10.1007/s11547-015-0590-5. PMid:26493688.
28. Carrasco Cubero C, Chamizo Carmona E, Vela Casasempere P. Systematic review of the impact of drugs on diffuse interstitial lung disease associated with rheumatoid arthritis. Reumatol Clin (Engl Ed). 2021;17(9):504-13. http://dx.doi.org/10.1016/j.reuma.2020.04.015. PMid:34756311.
29. Ibfelt EH, Jacobsen RK, Kopp TI, Cordtz RL, Jakobsen AS, Seersholm N, et al. Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. Rheumatology. 2021;60(1):346-52. http://dx.doi.org/10.1093/rheumatology/keaa327. PMid:32780828.
30. 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. http://dx.doi.org/10.1183/13993003.00337-2020. PMid:32646919.

J Bras Pneumol. 2022;48(6):e20220183
https://dx.doi.org/10.36416/1806-3756/e20220183

ORIGINAL ARTICLE

Circulating eosinophil levels and lung function decline in stable chronic obstructive pulmonary disease: a retrospective longitudinal study

Marcello Ferrari[1], Michela Pizzini[1], Lucia Cazzoletti[2], Valentina Ermon[1], Francesco Spelta[1], Sergio De Marchi[1], Luca Giuseppe Dalle Carbonare[1], Ernesto Crisafulli[1]

1. Dipartimento di Medicina, Unità di Medicina Interna e Medicina Respiratoria, Università di Verona, Verona (VR), Italia.
2. Dipartimento di Diagnostica e Sanità Pubblica, Università di Verona, Verona (VR), Italia.

Submitted: 27 May 2022.
Accepted: 20 September 2022.

Study carried out in the Unità di Medicina Interna e Medicina Respiratoria, Università di Verona, Verona (VR), Italia.

ABSTRACT

Objective: Whether blood eosinophils (bEOS) in chronic obstructive pulmonary disease (COPD) are associated with disease progression is a topic of debate. We aimed to evaluate whether the differential white blood cell (WBC) count, symptoms and treatment may predict lung function decline and exacerbations in COPD patients. **Methods:** We retrospectively examined stable COPD patients with a minimum follow-up of 3 years at our outpatients' clinic. We collected information about lung volumes (FEV_1, FVC), the total and differential WBC count, acute exacerbations of COPD (number in the 12 months before the beginning of the study=AE-COPD-B, and during the follow-up=AE-COPD-F), smoking status and treatment. FEV_1 decline and AE-COPD-F were described by using a generalized linear model and a 2-level random intercept negative binomial regression, respectively. The models included eosinophil and neutrophil counts as potential predictors and were adjusted by sex, age, smoking status, AE-COPD-B, treatment with bronchodilators and inhaled corticosteroids (ICS). **Results:** Sixty-eight patients were considered, 36 bEOS- (<170 cells/μL, the median value) and 32 bEOS+ (≥170 cells/μL). ΔFEV_1 was higher in bEOS+ than bEOS- (34.86 mL/yr vs 4.49 mL/yr, p=0.029). After adjusting for potential confounders, the eosinophil count was positively (β=19.4; CI 95% 2.8, 36.1; p=0.022) and ICS negatively (β=-57.7; CI 95% -91.5,-23.9; p=0.001) associated with lung function decline. bEOS were not found to be associated with the number of AE-COPD-F. **Conclusion:** In stable COPD patients, a higher level of blood eosinophils (albeit in the normal range) predicts a greater FEV_1 decline, while ICS are associated with a slower progression of airflow obstruction.

Keywords: COPD; Blood eosinophils; FEV_1 decline; Exacerbations; Biomarkers.

INTRODUCTION

Lung function decline is one of the most important features of the natural history in patients with Chronic Obstructive Pulmonary Disease (COPD). It is estimated that mean FEV_1 decline is about 20-40 mL/year and that there are two subgroups of patients, called "faster decliners" and "slower decliners"[1].

Systemic and pulmonary inflammation may contribute to this decline. The primary involvement of neutrophils, whose levels are higher in the airways of COPD patients and are positively associated with airflow obstruction is common knowledge.[2] Moreover, even if eosinophils are the predominant granulocyte population in subjects with asthma, recent evidence suggests the presence of eosinophilic inflammation in a subgroup of COPD patients.[3] Eosinophils in the airways correlate with their blood levels and this correlation, albeit weak, is significant.[4]

COPD patients have more circulating eosinophils than the non-COPD smoker population,[5] even though it is not clear whether this result is clinically relevant, as well as statistically significant. The blood eosinophil count can predict the risk of having an acute exacerbation. In the Copenhagen Study,[6] a blood eosinophil count with more than 340 cells/μL was associated with an almost 2 times higher risk of incurring severe exacerbations. In addition, the greatest risk of having an increased concentration of circulating eosinophils during exacerbations is related to a greater eosinophil count during the stability phase.[7]

The literature supports the notion that blood eosinophils could be a predictor of response to corticosteroid therapy in patients with acute exacerbations of COPD (AE-COPD).[7,8] During an acute exacerbation, COPD patients with an eosinophil count greater than 2% of the total white blood cells (WBC) have a low probability of relapse if they are treated with systemic corticosteroid.[9] However, there are no prospective randomized studies that examine the

Correspondence to:
Ernesto Crisafulli. Dipartimento di Medicina, Università di Verona, Largo L.A. Scuro, 10, 37134, Verona (VR), Italia.
Tel.: +39 045 8128146. E-mail: ernesto.crisafulli@univr.it
Financial support: None.

ISSN 1806-3756

role of the blood eosinophil count as a predictor of a response therapy during stable COPD.[10] Only few studies have investigated the association between the progression of airflow obstruction and blood eosinophils, with discordant results.[11-16] Thus, we conducted a longitudinal retrospective study aimed to investigate whether factors such as clinical characteristics, laboratory data and treatment were associated with FEV_1 decline over time, focusing our attention on the differential count of circulating leukocytes.

METHODS

We conducted a retrospective observational study using the last 5-year data in the database of the outpatient clinic at the University Hospital of Verona. A total of 239 patients with COPD were considered. The diagnosis was based on the GOLD criteria.[17] The study was approved by the Ethic Committee of our Institution.

We selected patients with the following characteristics: 1) a stable phase of the disease, i.e., no AE-COPD and no change in the treatment in the previous 3 months; 2) a blood eosinophil count lower than 450 cells/μL (upper normal limit of our laboratory); 3) a minimum follow-up of 3 years. We excluded patients with other lung diseases, such as lung cancer, interstitial lung diseases, asthma, pulmonary resection, and pulmonary infections. We also excluded patients with diseases related to atopy (such as rhinitis) and those with unacceptable spirometry.[18]

Demographic information, including sex, age, height, weight, and smoking habit were collected from the patient's medical record. Medical history and prescribed therapies for the respiratory disease (LABA, Long-acting β_2-Agonists; LAMA, Long-acting Muscarinic Antagonists; Inhaled Corticosteroids, ICS) were also recorded. A patient was on therapy with LABA, LAMA or ICS when he/she took these drugs (alone or in combination) at the beginning of the observation period.

The values of spirometry parameters (Forced Expiratory Volume in 1 second, FEV_1 L; Forced Vital Capacity, FVC L) were registered. Lung function decline (mL/year) was expressed as the FEV_1 value at the beginning minus the FEV_1 value at the end of the observational period, divided by the years of follow-up (ΔFEV_1, mL/yr).

Information on exacerbations, dyspnea (modified MRC scale[19]) were also available. An AE-COPD was defined as the worsening of respiratory symptoms requiring antibiotic or oral corticosteroid treatment.[17] AE-COPD-F was the number of exacerbations at the control visits performed during the follow-up period. AE-COPD-B was the number of exacerbations in the 12-months preceding the beginning of the period of observation.

Statistical analysis

The data are shown as means ± SD, or as median with interquartile range (IQR) as appropriate. The t-test or the Wilcoxon-Mann-Whitney test were used to assess the differences of continuous variables between groups of patients, accordingly. The chi-square test was used for the comparison of data expressed as percentages.

A multivariate generalized linear model was used to evaluate the association between the eosinophil and neutrophil blood count (independent variables) and ΔFEV_1 (mL/yr) (dependent variable), controlling for sex, age, smoking status (active smoker vs former smoker) (Model I). At a later stage, baseline treatment with bronchodilators, ICS and number of AE-COPD-B were included in the model (Model II).

The association between the eosinophil and neutrophil blood count (independent variables) and AE-COPD-F (dependent variable) was assessed by using a 2-level random intercept negative binomial regression, with level 1 units (visits) nested into level 2 units (patients), adjusting for sex and age at baseline (Model III). Another model was fitted to the data adding to the previous model as independent variables treatment with bronchodilators, treatment with ICS at baseline and number of AE-COPD-B (Model IV). The estimated coefficients of the negative binomial regression were expressed as incidence rate ratios (IRR) and 95% confidence intervals were provided. Model III and IV were not adjusted for smoking habits, because the number of current smokers at baseline was very limited (n=5 out of 68 COPD patients) and none of them reported exacerbations in the follow-up.

The goodness-of-fit was assessed using the Akaike information criterion (AIC)[20] and the Bayesian information criterion (BIC):[21] the best performances in predicting FEV_1 decline and the rate of exacerbations during follow-up were identified by the lowest AIC and BIC, when comparing model I with model II and model III with model IV.

The p value less than 0.05 was statistically significant.

The statistical analysis and graphs were processed using STATA/IC 16.1.

RESULTS

Two-hundred-and-thirty-nine medical records of COPD patients were analyzed. A total of 171 patients were excluded (Figure 1): 73 patients did not have a follow-up of at least 3 years (among them 11 had died); the blood eosinophil count of 75 patients was missing; 23 were not in a stable phase of the disease.

In total, 68 patients were included in the analysis (age 71.1±6.6 years; 18 (26.5%) females). The mean follow-up was 50.1±16.3 months. The median blood eosinophil count was 170 (IQR:115-260) cells per μL. Based on this value, the patients were divided into two groups, one with less than (36 patients, bEOS- group) and one with at least (32 patients, bEOS+) 170 blood eosinophils/μL.

The demographic and clinical characteristics of the COPD patients in the study are reported in the Table 1. Age, BMI, and male/female distribution were similar in the two groups. Active smokers were present in

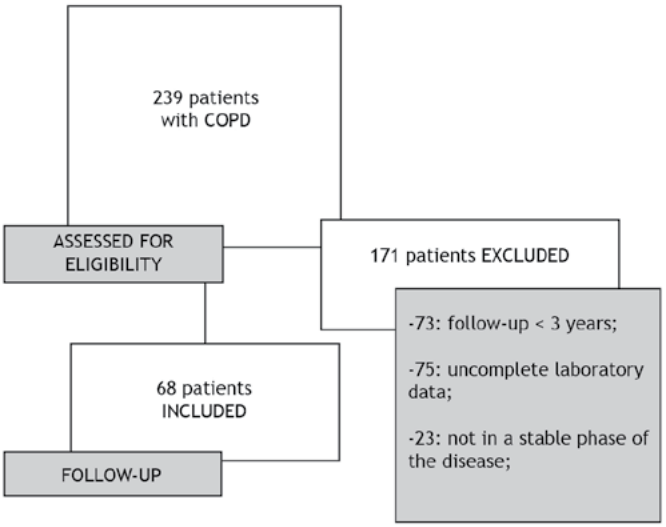

Figure 1. Selection of COPD patients in the study.

Table 1. Characteristics of the study population at baseline.

	Total (N= 68)	EOS – (N= 36)	EOS + (N= 32)	p value
Gender, n (%)				NS
- Male	50 (73.5%)	27 (75.0%)	23 (71.9%)	
- Female	18 (26.5%)	9 (25.0%)	9 (28.1%)	
Mean Age	71.0 (6.6)	71.0 (7.0)	71.1 (6.3)	NS
Median BMI (Kg/m^2)	26.7 (24.6;29.7)	25.3 (24.4;29.5)	27.5 (26.0;29.7)	NS
Median pack years	30.8 (10;48)	27.5 (0;46.5)	32 (16.5;60)	NS
Smoking Habit, n (%)				0.055*
- Ex-smoker	63 (92.6%)	31 (86.1%)	32 (100%)	
- Smoker	5 (7.4%)	5 (13.9%)	0 (0%)	
Median mMRC	1 (1;2)	1 (1;2)	1 (1;2)	NS
Chronic bronchitis, n (%)	26 (41.3%)	13 (39.4%)	13 (43.3%)	NS
Median AE-COPD-B	1 (0;2)	1 (0;2)	1 (0;2)	NS
LABA, n (%)	38 (61.3%)	18 (54.6%)	20 (69.0%)	NS
LAMA, n (%)	27 (43.6%)	14 (42.5%)	13 (44.8%)	NS
ICS, n (%)	22 (35.5%)	13 (39.4%)	9 (31.0%)	NS
Mean FEV_1 (L)	1.55 (0.67)	1.58 (0.72)	1.52 (0.62)	NS
Mean FEV_1 (% pred)	63.79 (21.37)	65.14 (23.14)	62.28 (19.5)	NS
Mean FVC (L)	2.86 (0.80)	2.85 (0.86)	2.89 (0.74)	NS
Mean FVC (% pred)	98.75 (21.23)	99.17 (22.18)	98.29 (20.47)	NS
Mean FEV_1/FVC (L)	52.91 (12.69)	53.90 (13.67)	51.81 (11.62)	NS
Median White blood cell count (10^9/µL)	7030 (5890;8080)	7040 (6030;7830)	6930 (5890;8280)	NS
Median Neutrophil count(10^9/µL)	3990 (3320;4990)	3960 (3430;5020)	4050 (2930;4900)	NS
Median Eosinophil count (10^9/µL)	170 (120;260)	130 (90;160)	270 (220;300)	<0.001
Median Lymphocyte count (10^9/µL)	1960 (1510;2450)	2050 (1500;2610)	1880 (1580;2300)	NS

Data are presented as mean ± SD or median (IQR). EOS-: eosinophil count < 170 cells/µL; EOS+: eosinophil count ≥ 170/µL; BMI: Body Mass Index; mMRC: modified Medical Research Council dyspnea scale; AE-COPD-B: Number of Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the 12 months prior the beginning of the study; LABA: Long-acting β_2-Agonists; LAMA: Long-acting Muscarinic Antagonists; ICS: Inhaled Corticosteroids; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity. *The Fisher test was used for this comparison because the expected counts were not greater than 5 in all cells.

the bEOS- group only, whereas the median value of pack year was higher, although not significantly, in the bEOS+ group. The number of AE-COPD-B tended to be higher in EOS+, even though the difference between

the groups was not statistically significant. The mMRC dyspnea scale and the use of LAMAs, LABAs and ICSs was comparable in bEOS+ and bEOS-. At the beginning of the study, the mean values of FVC, FEV_1 as well as leucocyte, neutrophil and lymphocyte counts were similar in the two groups.

When considering the whole sample, the mean ΔFEV_1 and the mean FVC annual decline resulted in 18.78 ± 58.25 mL/year and 9.5±125 mL/year, respectively. The ΔFEV_1 was significantly higher in bEOS+ (34.86±50.33) than bEOS- (4.49±61.69) (p=0.029). On the contrary, no statistically significant difference was found in terms of the FVC annual change between the two groups (p=0.393). During the follow up, the median number of exacerbations was not significantly different between EOS+ and EOS- (median:0, IQR:0-2 in EOS- and median:0, IQR:0-1 in EOS+; p=0.868).

After adjusting for sex, age and smoking habits at baseline, the eosinophils turned out to be significantly associated with ΔFEV_1 either when only neutrophils and eosinophils were considered as possible determinants (β=16.9; CI 95% 2.0,31.8; p=0.026) (Model I, Table 2) or in the complete model (β=19.4; CI 95% 2.8,36.1; p=0.022) (Model II, Table 2). Figure 2 shows the observed and adjusted mean of ΔFEV_1 by eosinophil count in the complete model: in the case of an increase in the eosinophil count of 100 cells per µL the FEV_1 decline was expected to increase by 19.4 mL/y. ICS treatment was found to be associated with a reduced lung function decline (β=-57.7; CI 95% -91.5,-23.9; p=0.001) (Model II, Table 2).

After adjusting for sex and age at baseline, the neutrophil count was found to be significantly associated with the number of AE-COPD-F when only neutrophils and eosinophils were considered as possible determinants: the estimated rate ratio of exacerbations for an increase in the neutrophil count of 100 cells/µL was 1.03 (CI 95% 1.00,1.07; p=0.032), i.e. holding all other variables in the model constant, the increase in the neutrophil count seems to increase the expected number of exacerbations by 3%. When baseline treatment with bronchodilators and with ICS and AE-COPD-B were included in the model (Model IV, Table 3), neither the eosinophil nor the neutrophil counts were significantly associated with the rate of exacerbations, whereas baseline treatment with bronchodilators resulted in a significant increase in the rate of exacerbations (estimated IRR=15.02, CI 95% 1.65,136.67).

The complete models (Model II and Model IV) had the best fitness, as shown by the lowest AIC and BIC (Table 2, Table 3).

DISCUSSION

The results of this retrospective, longitudinal study in COPD patients show that blood eosinophils are associated with a faster decline in FEV_1. On the contrary, the blood eosinophil count does not predict a higher risk of exacerbations.

The association between eosinophilic inflammation and lung function decline has been investigated in few studies with contrasting results. One study, in agreement with our results, found that an eosinophil blood count greater than 2% was associated with

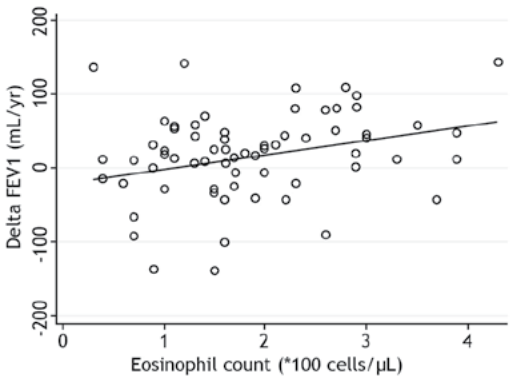

Figure 2. Observed (hollow circles) and adjusted mean (line) of delta FEV_1 by Eosinophil count (*100 cells/µL). The means are adjusted for age at baseline, sex, smoking status (active smoker vs former smoker), bronchodilator use, ICS use and baseline number of exacerbations.

Table 2. Multivariate Linear Regression Model, considering FEV_1 decline over time (ΔFEV_1, mL/yr) as the outcome.

	Model I			Model II		
Dependent variable: Δ FEV_1 (mL/yr)	β	CI 95%	p value	β	CI 95%	p value
Eosinophils (100 cells/µL)	16.9	2.0,31.8	0.026	19.4	2.8,36.1	0.022
Neutrophils (100 cells/µL)	0.2	-1.0,1.3	0.795	0.8	-0.4,1.9	0.192
Bronchodilator				23.6	-14.7,61.9	0.227
ICS				-57.7	-91.5,-23.9	0.001
AE-COPD-B				1.7	-11.4,14.9	0.797
Goodness of fit measures						
AIC		10.968			10.881	
BIC		193171.6			126148.3	

Model adjusted for age at baseline, sex, smoking status (active smoker vs former smoker).

Table 3. Multivariate Linear Regression Model, considering the number of exacerbations in the previous 12 months during follow up period (AE-COPD-F, N°/yr) as the outcome.

	Model III			Model IV		
Dependent variable: Number of exacerbations during follow up	IRR	CI 95%	p value	IRR	CI 95%	p value
Eosinophils (100 cells/μL)	1.28	0.87,1.90	0.214	1.15	0.75,1.74	0.524
Neutrophils (100 cells/μL)	1.03	1.00,1.07	0.032	1.01	0.98,1.04	0.393
Bronchodilator				15.02	1.65,136.67	0.016
ICS				1.06	0.45,2.52	0.889
AE-COPD-B				1.33	0.94,1.88	0.113
Goodness of fit measures						
AIC		295.852			257.894	
BIC		315.066			284.338	

Model adjusted for age at baseline and sex.

a faster decline of FEV_1.[11] Also, in a more recent paper,[15] it was shown that a blood eosinophil count of ≥300 cells/μL was an independent risk factor for accelerated lung function decline in a large Canadian cohort of older adults from the general population. On the contrary, in the ECLIPSE study,[13] COPD patients with a blood eosinophil count higher or lower than 2% had a similar FEV_1 decline in the 3-year follow-up. The HOKKAIDO COPD cohort study[14] reported that COPD patients with higher levels of circulating eosinophils maintained FEV_1 levels that were substantially stable over a period of 5 years, whereas a higher emphysema level and a greater circulating neutrophil count were predictors for a more rapid FEV_1 decline. Ethnic and environmental differences between our and the Japanese study may account for the contrasting results. More recently, one study[22] demonstrated that in COPD patients with a high blood eosinophil count (≥350 cells/μL), the exacerbations were associated with the subsequent acceleration of FEV_1 decline. In addition, the association between eosinophils in the sputum and lung function decline is uncertain. One study[23] found that both the neutrophil and eosinophil count in the sputum were related to FEV_1 decline in COPD. Another study[24] reported the association between eotaxin-1 (a chemokine inducing eosinophil activation) in lung lavage and a faster progression of the disease in COPD patients.[11]

We failed to find an association between the blood eosinophil count and the risk of exacerbation, in agreement with two group of authors,[25,26] but in contrast to other studies reporting a role of circulating eosinophils in predicting the onset of AE-COPD.[27-30] In the present study, the circulating neutrophil count was associated with exacerbations during the follow-up, although this was true only in the model in which sex and age, but not treatments, were considered as confounders. This result partially supports a recent study suggesting that a high blood neutrophil count may provide a useful indicator of the risk of exacerbations in COPD patients.[31]

Our retrospective study does not reach reliable conclusions regarding the possible effect of inhaled drugs on the decline of respiratory function and exacerbations. However, it is worth noting the finding of a negative association between ICS and FEV_1 decline, which may suggest a slowing-down effect of inhaled corticosteroids on the disease progression. The positive association between treatment with bronchodilators and the rate of exacerbations during the follow-up has no clear explanation. In our study, almost all patients were treated with a combination of drugs and only a minority of them were being treated with either LAMA or LABA alone, so that we are unable to evaluate the separate effect of the two types of bronchodilators. While keeping in mind this limit, we hypothesize that patients with more frequent exacerbations at baseline, and consequently with a higher risk of developing exacerbations in the follow-up, are more frequently treated. The use of medications may also explain the lack of an association between AE-COPD-B and AE-COPD-F. We are aware that only prospective, randomized studies are necessary to definitively clarify this point.

The blood eosinophil count is influenced by several factors, such as diurnal, seasonal, and hormonal variations.[32,33] Moreover, fluctuation in the disease and treatment may increase this variability.[32] Therefore, it has been pointed out that a single estimation of the eosinophil count, as in the case of our study, would be unlikely to reflect the overall pattern of blood eosinophilia.[34] However, a group of authors have shown that the proportion of COPD patients with a stable eosinophil count in a six-month time interval is high (93%) for subjects with a mean age of 70 years.[5] The variability is even more limited for an absolute eosinophil count lower than 340 cells/μL, which is similar to that found in our patients.[5] Finally, in the present study the eosinophil count was measured in a stable phase of the disease, at the same hour of the day, after an overnight fasting, all factors that may have further reduced the count variability.

Our study has some limitations. Other than the ones connected to its retrospective observational design, the choice of selecting patients in a stable phase of disease and the numerous exclusion criteria prevent from extending the findings to COPD patients with

different characteristics. Another limitation is the small number of the patients, that may explain the lack of some associations, such as between eosinophils and exacerbations. However, the sample size was large enough to support the hypothesis of a relationship between eosinophils and FEV_1 decline.

We considered an exacerbation to be ongoing when the patient reported the use antibiotics or corticosteroid after the worsening of symptoms, regardless of admission to an emergency room or hospitalization. Therefore, our results cannot be applied to the severe exacerbations (i.e., requiring hospitalization) or to the mild ones (i.e., those producing only a slight variation of the usual treatment).

We acknowledge that FEV_1 decline was calculated on only two points at the beginning and at the end of the observational period. A higher number of measurements might have provided a more reliable value of functional change. However, lung function tests were performed during a stable phase of disease, adopting the criteria of the ATS technical statement,[16] a fact that enabled us to obtain high quality data.

In conclusion, our results suggest that in patients with stable COPD, a higher level of blood eosinophils (albeit in the normal range) predicts a greater decline in FEV_1 over time, but not a higher number of exacerbations. Furthermore, ICS therapy seems to attenuate the progression of airflow obstruction, even though prospective randomized studies are needed to confirm these results.

AUTHOR CONTRIBUTIONS

MF, MP, LC: conception and design of the study. MF, MP, LC, VE, FS, SDM, LGDC, EC: acquisition, analysis, or interpretation of data. MF, MP, LC, LGDC, EC: drafting the work or revising it critically for important intellectual content. MF, LC, EC: approval of the final version of the manuscript.

REFERENCES

1. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365(13):1184-92. http://dx.doi.org/10.1056/NEJMoa1105482. PMid:21991892.
2. Stockley JA, Walton GM, Lord JM, Sapey E. Aberrant neutrophil functions in stable chronic obstructive pulmonary disease: the neutrophil as an immunotherapeutic target. Int Immunopharmacol. 2013;17(4):1211-7. http://dx.doi.org/10.1016/j.intimp.2013.05.035. PMid:23994347.
3. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2016;138(1):16-27. http://dx.doi.org/10.1016/j.jaci.2016.05.011. PMid:27373322.
4. Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMCSI cohort. Lancet Respir Med. 2017;5(12):956-67. http://dx.doi.org/10.1016/S2213-2600(17)30432-0. PMid:29146301.
5. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, et al. Stability of blood eosinophils in patients with chronic obstructive pulmonary disease and in control subjects, and the impact of sex, age, smoking, and baseline counts. Am J Respir Crit Care Med. 2017;195(10):1402-4. http://dx.doi.org/10.1164/rccm.201701-0009LE. PMid:28165763.
6. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. the copenhagen general population study. Am J Respir Crit Care Med. 2016;193(9):965-74. http://dx.doi.org/10.1164/rccm.201509-1869OC. PMid:26641631.
7. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2012;186(1):48-55. http://dx.doi.org/10.1164/rccm.201108-1553OC. PMid:22447964.
8. Brightling CE, McKenna S, Hargadon B, Birring S, Green R, Siva R, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. Thorax. 2005;60(3):193-8. http://dx.doi.org/10.1136/thx.2004.032516. PMid:15741434.
9. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. Eur Respir J. 2014;44(3):789-91. http://dx.doi.org/10.1183/09031936.00062614. PMid:24925917.
10. Bafadhel M, Peterson S, de Blas MA, Calverley PM, Rennard SI, Richter K, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med. 2018;6(2):117-26. http://dx.doi.org/10.1016/S2213-2600(18)30006-7. PMid:29331313.
11. Rogliani P, Puxeddu E, Ciaprini C, Ora J, Onorato A, Pezzuto G, et al. The time course of pulmonary function tests in copd patients with different levels of blood eosinophils. BioMed Res Int. 2016;2016:4547953. http://dx.doi.org/10.1155/2016/4547953. PMid:27822474.
12. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characterist. Eur Respir J. 2014;44(6):1697-700. http://dx.doi.org/10.1183/09031936.00162414. PMid:25323230.
13. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008;31(4):869-73. http://dx.doi.org/10.1183/09031936.00111707. PMid:18216052.
14. Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, et al. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185(1):44-52. http://dx.doi.org/10.1164/rccm.201106-0992OC. PMid:22016444.
15. Tan WC, Bourbeau J, Nadeau G, Wang W, Barnes N, Landis SH, et al. High eosinophil counts predict decline in FEV1: results from the CanCOLD study. Eur Respir J. 2021;57(5):2000838. http://dx.doi.org/10.1183/13993003.00838-2020. PMid:33303555.
16. Park HY, Chang Y, Kang D, Hong YS, Zhao D, Ahn J, et al. Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study. Eur Respir J. 2021;58(4):2003823. http://dx.doi.org/10.1183/13993003.03823-2020. PMid:33737406.
17. GOLD: Global Initiative for Chronic Obstructive Lung Disease [Internet]. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 Report). [cited 2021 Dec 19]. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf
18. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-88. http://dx.doi.org/10.1164/rccm.201908-1590ST. PMid:31613151.
19. Ong KC, Earnest A, Lu SJ. A multidimensional grading system (BODE index) as predictor of hospitalization for COPD. Chest. 2005;128(6):3810-6. http://dx.doi.org/10.1378/chest.128.6.3810. PMid:16354849.
20. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr. 1974;19(6):716-23. http://dx.doi.org/10.1109/TAC.1974.1100705.
21. Schwarz G. Estimating the dimension of a model. Ann Stat [serial on the Internet]. 1978 [cited 2021 Dec 19];6(2):461-64. Available from: http://www.jstor.org/stable/2958889
22. Kerkhof M, Voorham J, Dorinsky P, Cabrera C, Darken P, Kocks JWH, et al. Association between COPD exacerbations and lung function

decline during maintenance therapy. Thorax. 2020;75(9):744-53. http://dx.doi.org/10.1136/thoraxjnl-2019-214457. PMid:32532852.

23. Donaldson GC, Seemungal TA, Patel IS, Bhowmik A, Wilkinson TM, Hurst JR, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995-2004. http://dx.doi.org/10.1378/chest.128.4.1995. PMid:16236847.
24. D'Armiento JM, Scharf SM, Roth MD, Connett JE, Ghio A, Sternberg D, et al. Eosinophil and T cell markers predict functional decline in COPD patients. Respir Res. 2009;10(1):113. http://dx.doi.org/10.1186/1465-9921-10-113. PMid:19925666.
25. Singh D, Wedzicha JA, Siddiqui S, de la Hoz A, Xue W, Magnussen H, et al. Blood eosinophils as a biomarker of future COPD exacerbation risk: pooled data from 11 clinical trials. Respir Res. 2020;21(1):240. http://dx.doi.org/10.1186/s12931-020-01482-1. PMid:32943047.
26. Miravitlles M, Monteagudo M, Solntseva I, Alcázar B. Blood eosinophil counts and their variability and risk of exacerbations in COPD: a population-based study. Arch Bronconeumol (Engl Ed). 2021;57(1):13-20. http://dx.doi.org/10.1016/j.arbres.2019.12.015. PMid:32061402.
27. Cheng SL, Lin CH. Effectiveness using higher inhaled corticosteroid dosage in patients with COPD by different blood eosinophilic counts. Int J Chron Obstruct Pulmon Dis. 2016;11:2341-8. http://dx.doi.org/10.2147/COPD.S115132. PMid:27703344.
28. Tashkin DP, Wechsler ME. Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2018;13:335-49. http://dx.doi.org/10.2147/COPD.S152291. PMid:29403271.
29. Prins HJ, Duijkers R, Lutter R, Daniels JM, van der Valk P, Schoorl M, et al. Blood eosinophilia as a marker of early and late treatment failure in severe acute exacerbations of COPD. Respir Med. 2017;131:118-24. http://dx.doi.org/10.1016/j.rmed.2017.07.064. PMid:28947018.
30. Zeiger RS, Tran TN, Butler RK, Schatz M, Li Q, Khatry DB, et al. Relationship of blood eosinophil count to exacerbations in chronic obstructive pulmonary disease. J Allergy Clin Immunol Pract. 2018;6(3):944-954.e5. http://dx.doi.org/10.1016/j.jaip.2017.10.004. PMid:29153881.
31. Lonergan M, Dicker AJ, Crichton ML, Keir HR, Van Dyke MK, Mullerova H, et al. Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. Respir Res. 2020;21(1):166. http://dx.doi.org/10.1186/s12931-020-01436-7. PMid:32611352.
32. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? Lancet Respir Med. 2017;5(9):747-59. http://dx.doi.org/10.1016/S2213-2600(17)30217-5. PMid:28601554.
33. Spector SL, Tan RA. Is a single blood eosinophil count a reliable marker for "eosinophilic asthma?". J Asthma. 2012;49(8):807-10. http://dx.doi.org/10.3109/02770903.2012.713428. PMid:22900679.
34. Hamad GA, Cheung W, Crooks MG, Morice AH. Eosinophils in COPD: how many swallows make a summer? Eur Respir J. 2018;51(1):1702177. http://dx.doi.org/10.1183/13993003.02177-2017. PMid:29371387.

J Bras Pneumol. 2022;48(6):e20210505
https://dx.doi.org/10.36416/1806-3756/e20210505

ORIGINAL ARTICLE

Clinical, laboratory, and radiographic aspects of patients with pulmonary tuberculosis and dysglycemia and tuberculosis treatment outcomes

André Luiz Bezerra[1], Adriana da Silva Rezende Moreira[1], Lorrayne Isidoro-Gonçalves[2], Carla F. dos Santos Lara[1,3], Gustavo Amorim[4], Elisangela C. Silva[1,5,6,7], Afrânio Lineu Kritski[1], Anna Cristina C. Carvalho[1,2]

1. Programa Acadêmico de Tuberculose, Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Laboratório de Inovações em Terapias, Ensino e Bioprodutos – LITEB – Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.
3. Serviço de Tisiologia, Centro Municipal de Saúde de Duque de Caxias, Secretaria Municipal de Duque de Caxias, Duque de Caxias (RJ) Brasil.
4. Department of Biostatistics, Vanderbilt University Medical Center, Nashville (TN) USA.
5. Laboratório de Micobacteriologia Molecular, Hospital Universitário Clementino Fraga Filho, Instituto de Doenças do Tórax – HUCFF-IDT – Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
6. Laboratório Reconhecer Biologia, Centro de Biociência e Biotecnologia, Universidade Estadual do Norte Fluminense Darcy Ribeiro, Campos dos Goytacases (RJ) Brasil.
7. Fundação Saúde do Estado do Rio de Janeiro, Secretaria de Saúde do Estado do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

Submitted: 22 February 2022.
Accepted: 19 August 2022.

Study carried out in the Serviço de Tisiologia, Centro Municipal de Saúde de Duque de Caxias, Secretaria Municipal de Duque de Caxias, Duque de Caxias (RJ) Brasil.

ABSTRACT

Objective: To analyze the association of dysglycemia with clinical, laboratory, and radiographic characteristics of patients with pulmonary tuberculosis (PTB), as well as with their tuberculosis treatment outcomes. **Methods:** This was a longitudinal study involving 140 patients diagnosed with PTB (positive cultures for *Mycobacterium tuberculosis* or positive Xpert MTB/RIF results from sputum samples). Patients were evaluated at diagnosis (M_0), after completing the second month of treatment (M_2), and at the end of treatment (M_{END}). At M_0, the patients were classified into three groups: normoglycemia+PTB (NGTB); pre-diabetes mellitus+PTB (PDMTB), and diabetes mellitus+PTB (DMTB), in accordance with glycated hemoglobin levels (< 5.7%, 5.7%-6.4%, and ≥ 6.5%, respectively). Treatment outcomes were classified as favorable (cure or treatment completion) and unfavorable (death, loss to follow-up, or treatment failure). **Results:** In our sample, 76 patients (61.4%) had dysglycemia, 20 of whom (14.3%) had DM at M_0. The patients with dysglycemia, in comparison with those in the NGTB group, more frequently presented with positive sputum smear microscopy (94.2% vs. 75.9%; p = 0.003); cavities (80.2% vs. 63.0%; p = 0.03); bilateral lesions (67.4% vs. 46.0%; p = 0.02); and higher median of affected thirds of the lungs (3.0 vs. 2.0; p = 0.03) on chest radiography. No significant differences regarding outcomes were found among the groups, but tuberculosis lethality was higher in the DMTB group than in the PDMTB and NGTB groups (20% vs. 2.2%). **Conclusions:** PTB patients with dysglycemia had laboratory and radiographic manifestations indicative of more advanced disease, and the risk of death was higher in the DMTB group. These findings reinforce the recommendation for early screening for DM in patients with newly diagnosed tuberculosis in order to reduce the risk of death during treatment.

Keywords: Tuberculosis/diagnosis; Tuberculosis/diagnostic imaging; Tuberculosis/therapy; Diabetes mellitus; Treatment outcome.

INTRODUCTION

In recent years, the association between diabetes mellitus (DM) and tuberculosis (DMTB) has been recognized as an important public health problem. DM increases the risk of developing active tuberculosis by 2-3 times, and patients with DMTB more often have unfavorable tuberculosis treatment outcomes when compared with tuberculosis patients without DM.[1-3] The innate and adaptive immune responses to *Mycobacterium tuberculosis* are altered in patients with DM, increasing the risk of either primary infection or reactivation of tuberculosis infection.[4] The hyperinflammatory host response associated with tuberculosis can cause hyperglycemia, hinder the clinical management of patients with DM, and induce the development of DM in patients with pre-DM.[5]

The progress made toward tuberculosis elimination has been recently affected by the COVID-19 pandemic, which resulted in reduced access to tuberculosis

Correspondence to:
Anna Cristina C. Carvalho. Laboratório de Inovações em Terapias, Ensino e Bioprodutos, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Avenida Brasil, 4365, Manguinhos, CEP 21040-900, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 2562-1050. E-mail: anna.carvalho@ioc.fiocruz.br
Financial support: This study received financial support from the *Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ, Carlos Chagas Filho Foundation for the Support of Research in the State of Rio de Janeiro; Grant no. 15/2014—*Programa de Cooperação Bilateral*/FAPERJ/Associação Columbia Global Center/Brasil—2014 [Bilateral Cooperation Program]). ALK is a senior scientist from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development). LIG is the recipient of a grant from the CNPq (Grant no. 115148/2020-5).

services, leading to an 18% drop in the number of newly diagnosed tuberculosis cases and increased numbers of tuberculosis-related deaths. These figures may be further hampered by the rapid increase in DM in recent years, particularly in low- and middle-income countries.[6] Prospective studies evaluating the role of dysglycemia (DM and pre-DM) in the clinical presentation of tuberculosis and response to tuberculosis treatment under routine conditions carried out in countries with a high tuberculosis burden are still scarce in the literature.[7,8] Data on DMTB provided by the Brazilian Ministry of Health[9] and based on reported tuberculosis cases to the *Sistema de Informação de Agravos de Notificação* (Brazilian Case Registry Database) showed that, between 2019 and 2021, 10% of the patients with tuberculosis reported to be diabetic.

In the present study, we aimed to describe the clinical, laboratory, and radiographic characteristics of pulmonary tuberculosis (PTB) patients with and without dysglycemia, as well as to analyze the association of these characteristics with tuberculosis treatment outcomes.

METHODS

Between September of 2016 and November of 2020, we carried out a longitudinal study involving patients with PTB treated at the Municipal Health Care Center in the city of Duque de Caxias, Brazil.

A consecutive, convenience sample of individuals seeking the center with cough for at least two weeks was screened for tuberculosis with the use of a clinical score[10] based on respiratory signs and symptoms suggestive of the disease. Patients with a score ≥ 5 had a medium/high probability of having PTB and were invited to participate in the study.[10] Patients who were ≥ 18 years of age and agreed to be interviewed, to undergo anthropometric measurements and chest radiography (CXR), and to have clinical samples collected were included in the study. Participants with a positive culture for *M. tuberculosis* and/or a positive Xpert MTB/RIF assay (GeneXpert; Cepheid, Sunnyvale, CA, USA) result from sputum samples were defined as having PTB. According to the glycated hemoglobin (HbA1c) profile, tuberculosis patients were categorized into three groups: normoglycemic group (NGTB; HbA1c < 5.7%); pre-diabetic group (PDMTB; 5.7% ≤ HbA1c ≤ 6.4%); and diabetic group (DMTB; HbA1c ≥ 6.5%).[11-13] All HbA1c assays were performed in a certified laboratory (*Laboratório de Análises Clínicas da Unigranrio*) in the city of Duque de Caxias.

After giving written informed consent, the patients were evaluated at the moment of receiving the diagnosis of tuberculosis or during the first week of tuberculosis treatment initiation (M_0), after completing the second month of treatment (M_2), and at the end of the treatment (M_{END}). During the visits, patients underwent anthropometric measurements (weight and height), sputum tests (sputum smear microscopy, Xpert MTB/RIF, culture for *M. tuberculosis*, first-line drug susceptibility testing [BACTEC MGIT 960 SIRE; Becton Dickinson, Sparks, MD, USA]), blood tests (fasting glycemia and HbA1c), and CXR. Participants also completed a questionnaire, administered by a trained nurse, with questions about sociodemographic characteristics, as well as signs and symptoms suggestive of PTB. Tobacco, alcohol, and illicit drug use was evaluated by a specific questionnaire.[14] A pulmonologist, blinded to the patients' glycemic profile, evaluated CXR by using a standardized form regarding the presence of lung cavities (number and size) and extension of lung involvement (unilateral or bilateral lesions and number of affected thirds of the lungs). Information on tuberculosis treatment outcomes was obtained from clinical records, and these outcomes were classified as favorable (cure or treatment completion) or unfavorable (death, loss to follow-up, or treatment failure).

Absolute and relative frequencies of categorical variables were calculated; for continuous variables, medians and interquartile ranges were described. Associations of categorical variables with dysglycemia and treatment outcome were assessed by the chi-square test (or Fischer's exact test, when indicated), and ORs and respective 95% CIs were described. To compare continuous variables, the Wilcoxon-Mann-Whitney test was used. The significance level was set at 5%, and p values were two-tailed. Multivariate analyses of the association of clinical, laboratory, and radiographic characteristics with HbA1c levels and tuberculosis treatment outcomes were performed using logistic regression. Box plots of the distribution of HbA1c levels at M_0, M_2 and M_{END}, as well as among patients who died or not, were built. For statistical analyses, the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA) and the R program 2019 (The R Foundation for Statistical Computing, Vienna, Austria) were used.

This study was approved by the Research Ethics Committee of the University Hospital Clementino Fraga Filho on 07/02/2015 (CAAE no. 45637715.5.0000.5257).

RESULTS

During the study period, 318 eligible patients with respiratory symptoms and medium/high clinical score results for PTB were identified. Of those 318 patients, 8 patients (3.8%) were excluded: 3 individuals were unable to collect or deliver a sputum sample and were referred to further investigation; blood samples were not collected from another 3; and it was not possible to process the samples sent to the laboratory from 2 participants. Of the 310 participants initially included in the study, 140 (45.2%) had a diagnosis of PTB.

Most PTB patients were male (n = 93; 66.4%); the medians of age and BMI were, respectively, 36 years and 19.7 kg/m^2. Non-White participants were more represented (n = 116; 82.9%), and 75 patients

(53.6%) attended school for less than 8 years. Tobacco, alcohol, and illicit drug use was identified, respectively, in 42.9%, 49.3%, and 24.3% of the patients (Table 1). Previous tuberculosis treatment and HIV infection were observed in 12.9% and 7.2%, respectively (Table S1).

The prevalence of dysglycemia among the patients at M_0 was 61.4% (pre-DM, in 47.1% and DM, in 14.3%). Among the 20 patients with DM, 13 (65.0%) had a previous diagnosis of type 2 DM. Blood glucose was measured in all patients; however, information on fasting was recorded only in 112 patients (80.0%). The test was performed after fasting in 73.2% (82/112), and in 11.0% (9/82) of these cases the values were ≥ 126 mg/dL. Of those 9 patients, 4 (44.4%) had a previous diagnosis of type 2 DM.

Age and BMI medians were significantly higher in the DMTB group. Higher use of tobacco, alcohol, and illicit drugs was observed in the PDMTB group (Table 1).

Regarding symptoms suggestive of PTB, previous tuberculosis treatment, and HIV infection, no statistical differences were observed between normoglycemic and dysglycemic patients with tuberculosis. Cough and sputum were reported by all patients, as both variables were included in the definition of individuals with respiratory symptoms, an eligibility criterion adopted in the study (Table S1).

CXR findings and microbiological and molecular test results at diagnosis of PTB and during follow-up

At diagnosis of PTB, patients in the PDMTB group more frequently presented with cavitary disease on CXR (84.8%) when compared with those in the NGTB (63.0%) and DMTB (65.0%) groups. There were no statistical differences in the mean number of cavities and in the number of cavities larger than 2 cm among the three groups of patients. However, bilateral lesions were more frequently observed in the DMTB group than in the NGTB group (70% vs. 46%; p = 0.03). The mean number of thirds of the lungs affected was statistically higher in the DMTB and PDMTB groups than in the NGTB group. In patients with dysglycemia, in comparison with those in the NGTB group, cavities (80.2% vs. 63.0%) and bilateral lesions on CXR (67.4% vs. 46.0%) were more common, and there was also a higher number of affected thirds of the lungs (median, 3 vs. 2). During the follow-up period (M_2 and M_{END}), no statistical differences were observed in CXR findings among the three groups of patients (Table 2).

Positivity on sputum smear microscopy was significantly higher in the PDMTB and DMTB groups (93.0%) than in the NGTB group (75.9%; p = 0.005); however, positive Xpert MTB/RIF and *M. tuberculosis* culture results in sputum were similar among the groups (Table 3). Resistant *M. tuberculosis* strains were more common in the NGTB (20.9%) and PDMTB (19.0%) groups than in the DMTB group (10.0%). The most common drug resistance patterns were monoresistance to streptomycin (45.8%, 11/24) and to isoniazid (25.0%, 6/24). During follow-up, no significant differences were observed regarding microbiological test results in the three groups of patients (Table 3).

Univariate and multivariate analyses of clinical, radiographic, and microbiological characteristics associated with dysglycemia

Univariate and multivariate logistic regression analyses of clinical, radiographic, and microbiological

Table 1. Sociodemographic data of patients with pulmonary tuberculosis (N = 140), in accordance with glycated hemoglobin levels at the time of diagnosis.[a]

Variable		NGTB group (n = 54)	PDMTB group (n = 66)	p[b]	DMTB group (n = 20)	p[c]	p[d]
Sex	Female	16 (29.6)	23 (34.8)	0.56	8 (40.0)	0.41	0.46
	Male	38 (70.4)	43 (65.2)		12 (60.0)		
Age	years	33.5 [24.0-46.0]	35.5 [26.7-48.5]	0.29	44.0 [37.2-57.0]	0.01	0.08
Skin color	White	12 (22.2)	9 (13.6)	0.23	3 (15.0)	0.74	0.25
	Non-White	42 (77.8)	57 (86.4)		17 (85.0)		
Schooling	< 8 years	25 (46.3)	40 (60.6)	0.14	10 (50.0)	0.79	0.22
	≥ 8 years	29 (53.7)	26 (39.4)		10 (50.0)		
BMI	kg/cm^2	19.6 [17.2-21.1]	19.2 [18.2-21.5]	0.38	23.1 [20.0-26.6]	< 0.005	0.05
BMI	≥ 18.5 kg/cm^2	33 (61.1)	44 (66.7)	0.56	18 (90.0)	0.02	0.19
	< 18.5 kg/cm^2	21 (38.9)	22 (33.3)		2 (10.0)		
Tobacco	No	33 (61.1)	31 (47.7)	0.19	15 (75.0)	0.41	0.48
	Yes	21 (38.9)	34 (52.3)		5 (25.0)		
Alcohol	No	27 (50.0)	30 (46.2)[e]	0.71	13 (65.0)	0.30	1.00
	Yes	27 (50.0)	35 (53.8)[e]		7 (35.0)		
Illicit drugs	No	41 (75.9)	47 (72.3)[e]	0.68	17 (85.5)	0.53	1.00
	Yes	13 (24.1)	18 (27.7)[e]		3 (15.0)		

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; and DMTB: (DM; HbA1c ≥ 6.5%) + TB. [a]Values expressed as n (%) or median [IQR]. [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB+DMTB. [e]n = 65.

Table 2. Chest radiography findings in patients with pulmonary tuberculosis (N = 140) at diagnosis, after completing the second month of treatment, and at the end of tuberculosis treatment, in accordance with the levels of glycated hemoglobin.[a]

Finding M_0		NGTB group (n = 54)	PDMTB group (n = 66)	p[b]	DMTB group (n = 20)	p[c]	p[d]
Presence of cavity	Yes	34 (63.0)	56 (84.8)	0.01	13 (65.0)	1.00	0.03
	No	20 (37.0)	10 (15.2)		7 (35.0)		
Number of cavities		3.0 [1.0-4.0]	3.0 [2.0-4.0]	0.64	3.0 [1.0-6.0]	0.97	0.68
Cavity > 2 cm	Yes	33 (97.1)	52 (92.9)	0.64	13 (100)	1.00	1.00
	No	1 (2.9)	4 (7.1)		0 (0.0)		
Lesion[e]	Unilateral	27 (54.0)	22 (33.3)	0.03	6 (30.0)	0.11	0.02
	Bilateral	23 (46.0)	44 (66.7)		14 (70.0)		
Number of affected thirds		2.0 [2.0-3.2]	3.0 [2.0-4.0]	0.06	3.0 [2.2-4.5]	0.06	0.03
M_2		NGTB group (n = 27)	PDMTB group (n = 26)	p[b]	DMTB group (n = 11)	p[c]	p[d]
Presence of cavity	Yes	13 (48.1)	14 (53.8)	0.78	7 (63.6)	0.48	0.61
	No	14 (51.9)	12 (46.2)		4 (36.4)		
Number of cavities		2.0 [1.0-3.0]	2.0 [1.0-3.0]	0.79	2.0 [1.0-4.0]	0.91	0.87
Cavity > 2 cm	Yes	8 (61.5)	10 (71.0)	0.69	6 (85.7)	0.35	0.45
	No	5 (38.5)	4 (28.6)		1 (14.3)		
Lesion[f]	Unilateral	15 (57.7)	9 (34.6)	0.16	9 (90.0)	0.11	0.61
	Bilateral	11 (42.3)	17 (65.4)		1 (10.0)		
Number of affected thirds		2.0 [1.0-2.2]	2.0 [2.0-3.0]	0.09	2.0 [1.7-2.0]	0.71	0.13
M_{END}		NGTB group (n = 29)	PDMTB group (n = 35)	p[b]	DMTB group (n = 12)	p[c]	p[d]
Presence of cavity	Yes	5 (17.2)	7 (20.0)	1.00	1 (8.3)	0.65	1.00
	No	24 (82.8)	28 (80.0)		11 (91.7)		
Number of cavities		1.0 [1.0-2.5]	1.0 [1.0-2.0]	0.75	1.0 [1.0-1.0]	1.00	0.83
Cavity > 2 cm	Yes	4 (80.0)	5 (71.4)	1.00	1 (100)	1.00	1.00
	No	1 (20.0)	2 (28.6)		0 (0.0)		
Lesion[g]	Unilateral	13 (65.0)	10 (37.0)	0.08	10 (100)	0.06	0.57
	Bilateral	7 (35.0)	17 (63.0)		0 (0.0)		
Number of affected thirds		1.5 [1.5-2.0]	2.0 [1.0-2.0]	0.17	1.0 [1.0-2.0]	0.39	0.48

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; DMTB: (DM; HbA1c ≥ 6.5%) + TB; M_0: at diagnosis; M_2: after completing two months of treatment; and M_{END}: at the end of treatment. [a]Values expressed as n (%) or median [IQR]. [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB + DMTB. [e]n = 136. [f]n = 62. [g]n = 57.

characteristics at M_0 associated with dysglycemia are presented in Table 4. Higher BMI, presence of cavities on CXR, and positive sputum smear microscopy were independently associated with dysglycemia among the patients with PTB.

Variation in HbA1c levels during tuberculosis treatment

The distributions of HbA1c levels (in %) assessed at M_0, M_2 and M_{END} are shown in Figure 1. A significant reduction in HbA1c above normal levels (≥ 5.7%) was observed at M_2, particularly in the PDMTB group (from 47% at M_0 to 14% at M_2), that is, among the 66 patients in the PDMTB group at M_0, dysglycemia was not confirmed at M_2 in 46 (70%). The median HbA1c levels in the PDMTB and DMTB groups, respectively, significantly decreased from M_0—5.9% [5.8-6.1%] and 9.7% [6.8-11.8%]—to M_2—5.4% [5.1-5.6%] and 8.1% [5.9-12.5%]—to M_{END}—5.4% [5.2-5.7%] and 8.4% [6.3-10.3%]. We found a significant reduction in dysglycemic levels at M_2 compared with those at M_0 (61% vs. 25%; p = 0.001), which stabilized between M_2 and M_{END} (25% vs. 28%; p = 1.0). However, among 8 of the patients in the PDMTB group at M_2, 5 (62.5%) already had HbA1c levels ≥ 5.7% at M_0.

Tuberculosis treatment outcomes

All patients used the standard regimen for tuberculosis treatment (including patients with isoniazid resistance, who had their treatment extended to nine months), and the mean duration of tuberculosis treatment (in months) in the NGTB, PDMTB, and DMTB groups, respectively, were 6.8, 6.2, and 7.1 months (p = 0.13). Information on tuberculosis treatment outcomes was available for all patients except 1 (referred to another clinic). Among the 139 patients evaluated, 29 were lost to follow-up, 2 had treatment failure, 102 had favorable treatment outcomes (7 cured and 95 completed treatment), and 6 died. There were no significant associations of sociodemographic, clinical, and laboratory variables with the treatment outcomes. Patients in the PDMTB

Table 3. Microbiological data of patients with pulmonary tuberculosis (N = 140) at diagnosis, after completing the second month of treatment, and at the end of tuberculosis treatment, in accordance with the levels of glycated hemoglobin.[a]

Variable		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
M_0		(n = 54)	(n = 66)		(n = 20)		
Xpert MTB/RIF in sputum[e]	Nondetectable	3 (5.7)	2 (3.0)	0.65	0 (0.0)	0.55	0.36
	Detectable	50 (94.3)	64 (97.0)		20 (100)		
Smear microscopy	Negative	13 (24.1)	5 (7.6)	0.01	1 (5.0)	0.09	0.005
	Positive	41 (75.9)	61 (92.4)		19 (95.0)		
Positive smear microscopy	< 3+	20 (48.8)	32 (52.5)	0.84	10 (52.6)	1.00	0.70
	3+	21 (51.2)	29 (47.5)		9 (47.0)		
MTB culture	Negative	3 (5.6)	1 (1.1)	0.32	0 (0.0)	0.55	0.29
	Positive	51 (94.4)	65 (98.5)		20 (100)		
Drug susceptibility testing[f]	Sensitive	38 (79.2)	51 (81.0)	1.00	18 (90.0)	0.41	0.81
	Resistant	10 (20.9)	12 (19.0)		2 (10.0)		
Drug resistance[f]	Rifampin	0 (0.0)	0 (0.0)	0.12	0 (0.0)	0.66	0.15
	Isoniazid	4 (8.3)	1 (1.6)		1 (5.0)		
	Ethambutol	1 (2.1)	0 (0.0)		0 (0.0)		
	Pyrazinamide	1 (2.1)	0 (0.0)		0 (0.0)		
	Streptomycin	2 (4.2)	8 (12.7)		1 (5.0)		
	Isoniazid + Streptomycin	2 (4.2)	3 (5.7)		0 (0.0)		
M_2		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
		(n = 25)	(n = 32)		(n = 9)		
Smear microscopy	Negative	19 (76.0)	26 (81.3)	0.74	7 (78.0)	1.00	0.76
	Positive	6 (24.0)	6 (18.8)		2 (22.0)		
Positive smear microscopy	< 3+	5 (83.3)	6 (100)	1.00	2 (100)	1.00	0.42
	3+	1 (16.7)	0 (0.0)		0 (0.0)		
MTB culture[g]	Negative	13 (72.0)	13 (87.0)	0.41	5 (83.0)	1.00	0.43
	Positive	5 (28.0)	2 (13.0)		1 (17.0)		
M_{END}		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
		(n = 13)	(n = 23)		(n = 3)		
Smear microscopy	Negative	12 (92.0)	22 (96.0)	1.00	3 (100)	1.00	1.00
	Positive	1 (8.0)	1 (4.0)		0 (0.0)		
Positive smear microscopy	< 3+	0 (0.0)	1 (100)	1.00	0 (0.0)	N/A	1.00
	3+	1 (100)	0 (0.0)		0 (0.0)	N/A	
MTB culture[h]	Negative	5 (83.0)	11 (100)	0.35	0 (0.0)		0.35
	Positive	1 (16.0)	0 (0.0)		0 (0.0)		

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; DMTB: (DM; HbA1c ≥ 6.5%) + TB; MTB: *Mycobacterium tuberculosis*; M_0: at diagnosis; M_2: after completing two months of treatment; and M_{END}: at the end of treatment. [a]Values expressed as n (%). [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB + DMTB. [e]n = 139. [f]n = 131. [g]n = 39. [h]n = 17.

Table 4. Univariate and multivariate analysis of clinical, radiographic, and microbiological characteristics at the time of diagnosis of tuberculosis associated with dysglycemia among patients with pulmonary tuberculosis.

Variable	Normoglycemia	Dysglycemia	Analysis	
	NGTB group	PDMTB + DMTB groups	Unadjusted	Adjusted
	(n = 54)	(n = 86)	OR (95% CI)	OR (95% CI)
Age, years	33.5 [24.4-45.0]	38.0 [27.0-50.8]	1.20 (0.95-1.52)	1.12 (0.86-1.46)*
Female sex	16 (29.6)	31 (36.0)	1.33 (0.64-2.82)	1.07 (0.48-1.46)
BMI, kg/m^2	19.6 [17.3-21.0]	19.9 [18.4-22.5]	1.11 (1.00-1.24)	2.36 (1.31-4.61)**
Positive smear microscopy	41 (75.9)	80 (93.0)	4.13 (1.50-12.07)	4.59 (1.38-17.75)
Cavity on chest radiography	34 (63.0)	69 (80.2)	2.37 (1.10-5.18)	2.81 (1.13-7.22)

[a]Values expressed as n (%) or median [IQR]. *OR considering an increment of 10 years. **OR considering an increment of 5 units of BMI.

and DMTB groups showed no significantly higher frequencies of unfavorable outcomes (death, treatment dropout, or treatment failure) when compared with those in the NGTB group (25.0% vs. 33.9%). At M_{END}, 12 patients in the PDMTB group had favorable outcomes (cure or treatment completion). Likewise, there was no significant difference between tuberculosis treatment outcomes (favorable or unfavorable) and HbA1c levels (p = 0.38). However, of the 6 patients who died, 4 were in the DMTB group. Tuberculosis lethality was 20% (4/20) among the patients in the DMTB group, whereas it was 2.2% in the PDMTB (1/46) and NGTB (1/45) groups. Despite the analysis limitation due to the small number of events, we observed a significant association between death and higher HbA1c levels (Figure 2).

DISCUSSION

In countries with a high tuberculosis burden such as Brazil, few prospective studies have analyzed the clinical, microbiological, and radiographic characteristics of PTB patients or the role of DM and pre-DM in PTB treatment outcomes.[8,10]

In our study, the frequency of DM among PTB patients (14.2%) was higher than that reported in another study in Brazil[8] and closer to those reported in other series (from 12.8% to 25%),[16-19] but lower than that reported in a study conducted in India,[15] in which the proportion of patients with tuberculosis and DM was 30%. In countries such as China[20] and Kenya,[21] the frequency of the DMTB association has been found to be lower (5.0% and 6.3%, respectively) than that found in our study. In other studies carried out in Brazil, the frequency of DM among tuberculosis patients was similar to our findings (13.6% and 14%).[22,23] The differences in the prevalence of DM observed in those studies, carried out in different geographical regions, may be associated with genetic predispositions to DM, dietary habits (including alcohol consumption), obesity, age distribution, and sedentary lifestyle, but they may also be due to diverse methods to evaluate dysglycemia.[15-23]

Although the screening for DM in patients with tuberculosis at the beginning of treatment is internationally recommended, the test to be used (fasting glucose, glucose tolerance test, or HbA1c) and the timing of repeat testing may vary according to local conditions.[24-26] In our study, the information on fasting glycemia was collected in only 58.6% of the patients. Therefore, we chose to use HbA1c as a screening test, considering levels ≥ 6.5% as the criterion for DM diagnosis.[11,13,27] The use of HbA1c as a screening test for DM has some advantages, such as not requiring the patient to fast and having greater pre-analytical stability. However, the test has limitations: it is more expensive and influenced by other conditions (age, ethnicity, and presence of anemia).[27] Moreover, HbA1c testing can detect up to a third less DM cases when compared with a blood glucose fasting level ≥ 126 mg/dL.[28]

Symptoms of tuberculosis in patients with DM appear to be more common and severe than do those described in patients with tuberculosis without DM.[22,29] However, we found no significant differences regarding the typology or duration of symptoms between the NGTB group and the dysglycemic groups in our cohort. Patients with DMTB had a higher mean age and BMI (suggestive of overweight), which is a common finding in patients with type 2 DM, as reported in other studies.[16,21,24]

CXR findings in patients with the DMTB are more frequently associated with the presence of multiple cavities and bilateral pulmonary involvement. Patients

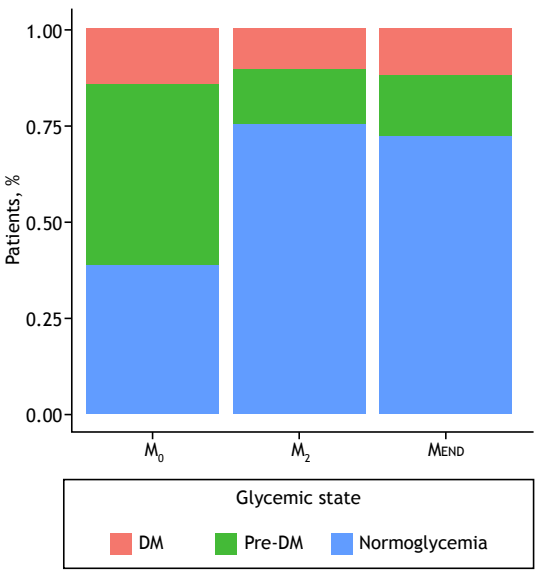

Figure 1. Proportion of patients diagnosed with pulmonary tuberculosis regarding glycemic state (determined by glycated hemoglobin levels) at three moments of evaluation: at the diagnosis of tuberculosis (M_0; n = 140); after completing the second month of treatment (M_2; n = 99); and at the end of tuberculosis treatment (M_{END}; n = 86). DM: diabetes mellitus.

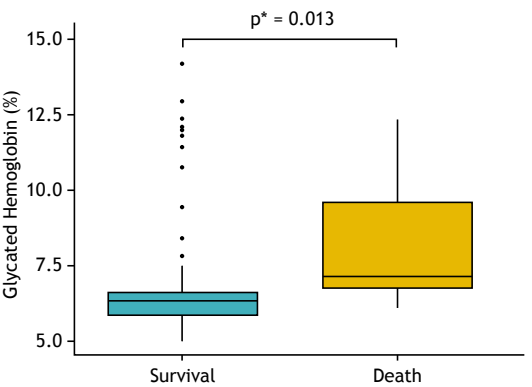

Figure 2. Box plots showing glycated hemoglobin levels at the diagnosis of pulmonary tuberculosis in patients with pulmonary tuberculosis whose outcome was survival or death. *Nonparametric Wilcoxon-Mann-Whiney test.

with DMTB also have a higher frequency of "atypical" findings on CXR, with lesions in the lower lobes, especially in patients with poor glycemic control.[30-32] In our sample, the presence of cavities, bilateral lesions, and involvement of a greater number of thirds of the lungs were more common among dysglycemic patients. As there are scarce data on the radiographic and inflammatory profiles of DMTB patients during tuberculosis treatment,[33] our findings corroborate the results described in one study[34] involving guinea pigs with chronic hyperglycemia and showing a lower innate immune response in the presence of alveolar macrophages infected by *M. tuberculosis*. The animals presented a delay in the specific T response and subsequent hyperinflammation, with high levels of Th1, Th2, and Th17 cytokines; neutrophilia; and high pulmonary bacillary load.[34] The fact that sputum smear microscopy is more frequently positive in dysglycemic patients might be a consequence of a reduced control in *M. tuberculosis* multiplication. In case series in India[17] and in China,[20] higher proportions of positive sputum smear microscopy were also reported among diabetic patients.

No differences regarding the use of alcohol, tobacco, or illicit drugs were found among the groups studied, corroborating what has been described in other studies.[19,20] However, studies carried out in Brazil[22,29] identified a higher frequency of tobacco use in patients with DMTB than in those with tuberculosis without DM. In a cohort of tuberculosis patients in South Korea, the risk of death was almost five-fold greater in the presence of DM and tobacco use.[35]

The differences in radiographic and microbiological findings observed between normoglycemic and dysglycemic patients at the diagnosis of tuberculosis were no longer present during follow-up. However, the analysis of radiographic and microbiological examinations during follow-up involved a smaller number of patients, and, therefore, our sample might have lacked power to identify such differences. In addition, the high proportion of deaths in the DMTB group (20%) might indicate a less effective response to antituberculosis therapy in patients with DMTB. The duration of tuberculosis treatment for patients with DMTB recommended by most guidelines,[24,36] including the Brazilian recommendations,[37] is the same for patients with tuberculosis without DM. However, patients with DMTB usually have a higher risk of toxicity to antituberculosis drugs (peripheral neuropathy due to isoniazid and ocular neuropathy due to ethambutol), drug interactions (in particular, rifampin), and low plasma concentrations of antituberculosis drugs.[38] All of these factors might contribute to unfavorable treatment outcomes in these patients.

In our study, pre-DM was identified in 47.1% of the patients with tuberculosis, which was higher than that described in other studies, with prevalences ranging from 7.4% to 37.5%.[8,16,17,19-21] However, we observed a significant reduction in HbA1c levels in the second month of treatment. Normalization of glycemic levels during tuberculosis treatment in initially dysglycemic patients has also been reported by other authors.[19,39,40] In the study by Calderon et al. carried out in Peru,[19] the prevalence of pre-DM patients decreased from 31% at the diagnosis of tuberculosis to 17% after completing the second month of treatment, maintaining the same proportion at the sixth month of treatment. These findings suggest that dysglycemia identified at the time of diagnosis is partially due to stress-induced hyperglycemia, a consequence of the inflammatory response to *M. tuberculosis*, which gradually decreases in consequence of infection control.[29,40]

Tuberculosis treatment outcomes were not significantly different between normoglycemic and dysglycemic patients. The reason for the lack of such differences might be due to the inclusion of a nonbiological variable, such as loss to follow-up, among the unfavorable outcomes. However, when analyzing the cases that progressed to death, there was higher lethality among the patients in the DMTB group, and an association between higher levels of HbA1c and death was observed. The association between DM and death during tuberculosis treatment was previously described in a systematic review and in a systematic review and meta-analysis,[2,3] in which the OR for death/treatment failure ranged from 1.69[2] to 1.88.[3]

Our study has limitations that are mainly related to the sample size, which might have limited the detection of significant associations, particularly during follow-up, when there was a further reduction in the number of participants. Furthermore, by including only patients with a medium/high probability of PTB using a clinical score for screening, we did not analyze patients with less exuberant symptoms, that is, in the early stages of the disease or with "atypical" presentations. Despite these limitations, the prospective nature of the study, with the collection of clinical, laboratory, and radiographic data at three different moments (M_0, M_2, and M_{END}) made it possible to assess the evolution of these parameters, such as the variation of HbA1c levels and their association with treatment outcomes.

In summary, we presented the results of a prospective cohort of patients with confirmed PTB, identifying high proportions of patients with associated DM and pre-DM, more advanced disease in patients with dysglycemia, and higher frequency of deaths among patients with the DMTB association. These findings reinforce the need for dysglycemia screening at the time of diagnosis of tuberculosis in order to identify patients with pre-DM and DM early, offering them treatment for both diseases. New prospective studies, involving a representative sample of patients with tuberculosis, are needed to understand the role of dysglycemic states in tuberculosis and in the risk of progression to DM.

AUTHOR CONTRIBUTIONS

ASRM and ACCC: conceptualization; data analysis; project administration; and drafting, editing, and

review of the manuscript. ALB: conceptualization; project administration; and drafting, editing, and review of the manuscript. ALK: conceptualization; funding acquisition; project administration; and drafting, editing, and review of the manuscript. CFSL: data collection; and editing and review of the manuscript. ECS: laboratory analysis; and editing and review of the manuscript. LIG: data collection; data analysis; and editing and review of the manuscript. GA: advanced statistical analysis; and editing and review of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health. 2010;15(11):1300-1314. https://doi.org/10.1111/j.1365-3156.2010.02632.x
2. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med. 2011;9:81. https://doi.org/10.1186/1741-7015-9-81
3. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019;23(7):783-796. https://doi.org/10.5588/ijtld.18.0433
4. Restrepo BI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis (Edinb). 2013;93 Suppl(0):S10-S14. https://doi.org/10.1016/S1472-9792(13)70004-0
5. Persistent inflammation during anti-tuberculosis treatment with diabetes comorbidity. Elife. 2019;8:e46477. https://doi.org/10.7554/eLife.46477
6. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2021 [cited 2021 Mar 8]. Global tuberculosis report 2021. Available from: https://www.who.int/publications/i/item/9789240037021
7. Calderon RI, Arriaga MB, Aliaga JG, Barreda NN, Sanabria OM, Barreto-Duarte B, et al. Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru. Int J Infect Dis. 2022;116:293-301. https://doi.org/10.1016/j.ijid.2022.01.012
8. Arriaga MB, Araújo-Pereira M, Barreto-Duarte B, Nogueira B, Freire MVCNS, Queiroz ATL, et al. The Effect of Diabetes and Prediabetes on Antituberculosis Treatment Outcomes: A Multicenter Prospective Cohort Study. J Infect Dis. 2022;225(4):617-626.
9. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; 2016 [cited 2021 Mar 8]. Sistema de Informação de Agravos de Notificação (SINAN): Tuberculose. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/tubercbr.def
10. Souza Filho JBOE, Sanchez M, Seixas JM, Maidantchik C, Galliez R, Moreira ADSR, et al. Screening for active pulmonary tuberculosis: Development and applicability of artificial neural network models. Tuberculosis (Edinb). 2018;111:94-101. https://doi.org/10.1016/j.tube.2018.05.012
11. Brasil. Ministério da Saúde. Biblioteca Virtual em Saúde [homepage on the Internet]; c 2014 [cited 2021 Mar 8]. Cadernos de Atenção Básica n. 35. Estratégias para o cuidado com da pessoa com doença crônica [Adobe Acrobat document, 162p.]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/estrategias_cuidado_pessoa_doenca_cronica_cab35.pdf
12. American Diabetes Association. Standards of Medical Care in Diabetes-2020. J Clin Appl Res Educ. 2020;43(Suppl 1). [Adobe Acrobat document, 224p.]. Available from: https://doi.org/10.2337/dc20-S012
13. World Health Organization [homepage on the Internet]. Geneva: World Health Organization, c2021 [updated 2006 Apr 21. cited 2021 Mar 8]. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Available from: https://www.who.int/publications/i/item/definition-and-diagnosis-of-diabetes-mellitus-and-intermediate-hyperglycaemia
14. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2021 Mar 8]. The ASSIST project - Alcohol, Smoking and Substance Involvement Screening Test - ASSIST Questionnaire Version 3.0 (Portuguese) [Adobe Acrobat document, 2p.] Available from: http://www.who.int/substance_abuse/activities/assist_portuguese.pdf
15. Viswanathan V, Kumpatla S, Aravindalochanan V, Rajan R, Chinnasamy C, Srinivasan R, et al. Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. PLoS One. 2012;7(7):e41367. https://doi.org/10.1371/journal.pone.0041367
16. Sarker M, Barua M, Guerra F, Saha A, Aftab A, Mahbub Latif AH, et al. Double Trouble: Prevalence and Factors Associated with Tuberculosis and Diabetes Comorbidity in Bangladesh. PLoS One. 2016;11(10):e0165396. https://doi.org/10.1371/journal.pone.0165396
17. Mave V, Meshram S, Lokhande R, Kadam D, Dharmshale S, Bharadwaj R. Prevalence of dysglycemia and clinical presentation of pulmonary tuberculosis in Western India. Int J Tuberc Lung Dis. 2017;21(12):1280-1287. https://doi.org/10.5588/ijtld.17.0474
18. Sharma B, Khanal VK, Jha N, Pyakurel P, Gurung GN. Study of the magnitude of diabetes and its associated risk factors among the tuberculosis patients of Morang, Eastern Nepal. BMC Public Health. 2019;19(1):1545. https://doi.org/10.1186/s12889-019-7891-x
19. Calderon RI, Arriaga MB, Lopez K, Barreda NN, Sanabria OM, Fróes Neto JF, et al. High prevalence and heterogeneity of Dysglycemia in patients with tuberculosis from Peru: a prospective cohort study. BMC Infect Dis. 2019;19(1):799. https://doi.org/10.1186/s12879-019-4416-2
20. Wang Q, Ma A, Han X, Zhao S, Cai J, Ma Y, et al. Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: a community based cohort study. PLoS One. 2013;8(12):e82660. https://doi.org/10.1371/journal.pone.0082660
21. Owiti P, Keter A, Harries AD, Pastakia S, Wambugu C, Kirui N, et al. Diabetes and pre-diabetes in tuberculosis patients in western Kenya using point-of-care glycated haemoglobin. Public Health Action. 2017;7(2):147-154. https://doi.org/10.5588/pha.16.0114
22. Almeida-Junior JL, Gil-Santana L, Oliveira CA, Castro S, Cafezeiro AS, Daltro C, et al. Glucose Metabolism Disorder Is Associated with Pulmonary Tuberculosis in Individuals with Respiratory Symptoms from Brazil. PLoS One. 2016;11(4):e0153590. https://doi.org/10.1371/journal.pone.0153590
23. Leal SB, Araújo GS, Nery JS, Santos CAST, Oliveira MG, Barreto ML, et al. Clinical and epidemiological aspects of cases of tuberculosis associated with diabetes in Salvador, Bahia, Brazil. Rev Soc Bras Med Trop. 2017;50(3):408-412. https://doi.org/10.1590/0037-8682-0409-2016
24. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2011 [cited 2021 Mar 8]. Collaborative Framework for Care and Control of Tuberculosis and Diabetes [Adobe Acrobat document, 53p.]. Available from: https://apps.who.int/iris/bitstream/handle/10665/44698/9789241502252_eng.pdf
25. Lin Y, Harries AD, Kumar AMV, Critchley JA, van Crevel R, Owiti P, et al. Management of Diabetes Mellitus-Tuberculosis. A Guide to the Essencial Practice [monograph on the Internet]. Paris: International Union Against Tuberculosis and Lung Disease; 2018 [cited 2021 Mar 8]. Available from: http://warn-carn-tb.org/wp-content/uploads/2019/03/TheUnion_Managment-DM-TB-en.pdf
26. Riza A, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabetes Endocrinol. 2014;2(9):740-753. https://doi.org/10.1016/S2213-8587(14)70110-X
27. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015;38 Suppl:S8-S16. https://doi.

org/10.2337/dc15-S005

28. Cowie CC, Rust KF, Byrd-holt DD, Gregg EW, Ford ES, Geiss LS, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. Diabetes Care. 2010;33(3):562-568. https://doi.org/10.2337/dc09-1524
29. Gil-Santana L, Almeida-Junior JL, Oliveira CA, Hickson LS, Daltro C, Castro S, et al. Diabetes Is Associated with Worse Clinical Presentation in Tuberculosis Patients from Brazil: A Retrospective Cohort Study. PLoS One. 2016;11(1):e0146876. https://doi.org/10.1371/journal.pone.0146876
30. Pérez-Guzman C, Torres-Cruz A, Villarreal-Velarde H, Salazar-Lezama MA, Vargas MH. Atypical radiological images of pulmonary tuberculosis in 192 diabetic patients: a comparative study. Int J Tuberc Lung Dis. 2001;5(5):455-461.
31. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-746. https://doi.org/10.1016/S1473-3099(09)70282-8
32. Jiménez-Corona EM, Cruz-Hervert LP, García-García L, Ferreyra-Reyes L, Delgado-Sánchez G, Bobadilla-Del-Valle M, et al. Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. Thorax. 2013;68(3):214-220. https://doi.org/10.1136/thoraxjnl-2012-201756
33. Kumar NP, Fukutani KF Shruthi BS, Alves T, Silveira-Matos OS, Rocha MS, et al Persistent inflammation during anti-tuberculosis treatment with diabetes comorbidity. Elife. 2019;8:e46477. https://doi.org/10.7554/eLife.46477
34. Vallerskog T, Martens GW, Kornfeld H. Diabetic mice display a delayed adaptive immune response to Mycobacterium tuberculosis. J Immunol. 2010;184(11):6275-6282. https://doi.org/10.4049/jimmunol.1000304
35. Reed GW, Choi H, Lee SY, Lee M, Kim Y, Park H, et al. Impact of diabetes and smoking on mortality in tuberculosis. PLoS One. 2013;8(2):e58044. https://doi.org/10.1371/journal.pone.0058044
36. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. https://doi.org/10.1093/cid/ciw376
37. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis, editors. Manual de recomendações para o Controle da Tuberculose no Brasil [monograph on the Internet]. 2nd ed. Brasília: Ministério da Saúde; 2019. [Adobe Acrobat document, 366 p.]. Available from: https://sbpt.org.br/portal/wp-content/uploads/2019/06/manual_recomendacoes_tb_2ed_atualizada_8maio19.pdf
38. Magis-Escurra C, Carvalho ACC, Kritski AL, Girardi E. Tuberculosis and Comorbidities. In: Tuberculosis. Sheffield, UK: European Respiratory Society; 2018.
39. Oluboyo PO, Erasmus RT. The significance of glucose intolerance in pulmonary tuberculosis. Tubercle. 1990;71(2):135-138. https://doi.org/10.1016/0041-3879(90)90010-6
40. Boillat-Blanco N, Ramaiya KL, Mganga M, Minja LT, Bovet P, Schindler C, et al. Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms. J Infect Dis. 2016;213(7):1163-1172. https://doi.org/10.1093/infdis/jiv568

J Bras Pneumol. 2022;48(6):e20220240
https://dx.doi.org/10.36416/1806-3756/e20220240

Clinical forms and diagnosis of tuberculosis in children and adolescents during the COVID-19 pandemic

Michely Alexandrino de Souza Pinheiro[1], Rafaela Baroni Aurilio[1], Ana Alice Amaral Ibiapina Parente[1,2], Maria de Fátima Bazhuni Pombo Sant'Anna[2], Ana Cristina Cisne Frota[1], Cristina Barroso Hofer[2], Thalita Fernandes de Abreu[2], Sidnei Ferreira[2], Clemax Couto Sant'Anna[2]

1. Instituto de Puericultura e Pediatria Martagão Gesteira. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.
2. Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.

Submitted:
Accepted:

Study carried out at the Instituto de Puericultura e Pediatria Martagão Gesteira - IPPMG - Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.

ABSTRACT

Objective: The present study aimed to describe the clinical forms and the time taken to diagnose new tuberculosis cases and to statistically analyze the isolated and combined forms of the disease in children and adolescents treated at a university hospital in Rio de Janeiro during the first year of the COVID-19 pandemic in Brazil. **Methods:** This was a cross-sectional study that used retrospective data on children (0–9 years old) and adolescents (10–18 years old) with pulmonary (PTB), extrapulmonary (EPTB), and combined tuberculosis (PTB + EPTB) followed up at the outpatient clinic from January 2019 to March 2021. Categorical data were analyzed by descriptive statistics and expressed as frequency and proportions. Categorical variables were compared using the Chi-square test, and numerical variables using Student's T-test. **Results:** A total of 51 cases were included, 63% (32/51) of which comprised patients in the year of the pandemic (group A), while 37% (19/51) were patients attended in previous years (group B). In group A, 19% (6/32) of the patients presented PTB, 59% (16/32) had EPTB, and 31% (10/32) had PTB+EPTB. In group B, 42% (8/19) of the patients presented PTB, 42% (8/19) had EPTB, and 16% (3/19) had PTB+EPTB. **Conclusion:** Our study revealed more tuberculosis cases in the first year of the pandemic than in the same period of the previous year, with greater variation of sites affected by the disease, including rarer and more severe forms.

Keywords: pandemic, children, adolescents, tuberculosis, coronavirus.

INTRODUCTION

Tuberculosis is a communicable disease that constitutes one of the leading causes of death worldwide. Since 1993, it has been considered a global emergency and a challenging public health problem. In 2019, approximately ten million people contracted tuberculosis, with 73,864 new cases in Brazil. At the end of that year, the global indicators of tuberculosis disease burden declined, and access to prevention and treatment improved.[1-3]

The coronavirus disease (COVID-19) pandemic has reversed years of progress. For the first time in more than a decade, the number of deaths due to tuberculosis has increased, and the reduced disease incidence achieved in previous years has decreased. Approximately half of the people with tuberculosis had no access to healthcare in 2020 and, therefore, were not reported. A recent study published by the Stop Tuberculosis Partnership organization showed that social isolation measures, which reduce the demand for services, may consequently lead to 6.3 million new cases and 1.3 million more deaths due to the disease by 2025. However, the impact of tuberculosis has been estimated to be much worse in 2021 and 2022.[3-6]

In 2020, economic and human health resources were reallocated due to the high priority of COVID-19, interrupting current health programs and reducing the early diagnosis and treatment of several diseases, including tuberculosis. The impact of the pandemic on the care of infectious diseases may have been greater in the area of pulmonary diseases than in others, as specialized teams concentrated their efforts to control COVID-19, thus dismantling specific tuberculosis services.[7] The negative impact of these measures could lead to an increase of up to 20% in the number of deaths by tuberculosis in the next five years.[6,8] Tuberculosis control measures have failed to achieve the global goals established by the United Nations (UN). Approximately 19.8 million people were treated for tuberculosis from 2018 to 2020, corresponding to only half of the 5-year goal of 40 million (2018–2022). In the same period, only 1.4 million children were treated, equivalent to 41% of the 5-year goal of 3.5 million. In 2020, the global

Correspondence to:
Michely Alexandrino de Souza Pinheiro. Instituto de Puericultura e Pediatria Martagão Gesteira-UFRJ. Rua Bruno Lobo, 50. Cidade Universitária. CEP 21941-612. Rio de Janeiro, RJ, Brasil. Tel.: +55 (21) 99209-0558 / +55 (21) 3776-0861. E-mail: medmichelypinheiro@gmail.com.
Financial support: CBH was supported by the Brazilian National Council for Scientific and Technological Development (Grant 304476/2018-8) and the Research Support Foundation of the State of Rio de Janeiro (Grants E26/200.843/2021 and E26/201.317/2016); CCS was supported by the National Council for Scientific and Technological Development (Grant 302973/2019-2) and the Research Support Foundation of the State of Rio de Janeiro (Grant E26/010.001877/2019).

ISSN 1806-3756

expenditure on tuberculosis services was US$5.3 billion, half of what is needed to control the disease, and preventive treatment decreased by 22% when compared to the previous year.[4] In Rio de Janeiro, there was a 16% increase in tuberculosis cases from 2015 to 2020, with 7,050 new cases in 2021. As for spatial distribution, the cases were more concentrated in areas of high population density and greater social vulnerability. The cure rates in laboratory-confirmed tuberculosis cases showed a significant decrease of 60.1% in 2020, with progressively increasing mortality (2019–2020) and treatment abandonment (2017–2021).[9]

The aim of the present study was to describe the clinical forms and the time taken to diagnose new tuberculosis cases and to statistically analyze the isolated and combined forms of tuberculosis in children and adolescents treated at a university hospital in Rio de Janeiro during the first year of the COVID-19 pandemic in Brazil.

METHODS

This cross-sectional study used retrospective data on children (0–9 years old) and adolescents (10–18 years old) with pulmonary (PTB), extrapulmonary (EPTB), and combined tuberculosis (PTB + EPTB) who were followed up at the pediatric pulmonology outpatient clinic of the Instituto de Puericultura e Pediatria Martagão Gesteira – (IPPMG), a reference university pediatric hospital in Rio de Janeiro, from January 1, 2019, to March 1, 2021.

The inclusion criteria were patients identified in the tuberculosis case registry book who were followed up at the IPPMG during the disease treatment period. Clinical and epidemiological data were obtained from medical records; patients whose medical records were not found were excluded.

The evaluated variables included disease history (fever, cough, weight loss, adynamia, dyspnea, and adenomegaly); contact with tuberculosis; diagnostic score of the Ministry of Health - Brazil (MoH-Brazil); alterations in chest radiography (lymph node hilum enlargement, miliary pattern, expansile pneumonia, cavitations, calcifications, pleural effusion, and atelectasis);[10] acid-fast bacilli (AFB) on Ziehl-Neelsen smears; culture of *Mycobacterium tuberculosis* (M.tb); Gene Xpert MTB-RIF and Gene Xpert Ultra tests (Cepheid – USA); tuberculin skin test (TST) positivity (≥ 5 mm); antibody tests for human immunodeficiency virus (HIV), and healthcare prior to PTB diagnosis (antibiotic therapy for common germs without improvement).

The diagnosis of PTB was established according to the MoH-Brazil clinical score (more than 40 points, very likely; 30–35 points, possible; less than 25 points, unlikely) based on epidemiological and clinical-radiological criteria, TST (positive ≥ 5 mm; negative < 5 mm), and bacteriological analyses.[11] The diagnosis of EPTB, in turn, was based on clinical and epidemiological criteria, TST, and invasive biopsy results compatible with tuberculosis. Patients with a diagnosis based on these criteria and whose response to treatment with antituberculosis drugs was satisfactory after two months of initiation were classified as having tuberculosis and included in the study.

The tuberculosis patients were divided into two groups: group A - from March 2020 to March 2021, corresponding to the first year of the COVID-19 pandemic; and group B - from January 2019 to February 2020, the period corresponding to the year before the pandemic.

The Gene Xpert MTB-RIF Ultra (Ultra) test was used when appropriate in patients in group A, and the Gene Xpert MTB-RIF (Xpert) test was used in patients in group B. Ultra's bacterial load detection is categorized as high, medium, low, and positive traces. In EPTB, positive traces indicate a positive M.tb result.[12]

Data were entered into a Microsoft Excel 12.0 (Office 2007) spreadsheet. The categorical data were analyzed by descriptive statistics and expressed as frequency and proportions, whereas non-categorical data were analyzed by numerical variables as minimum and maximum values and median and expressed as a box plot. Categorical variables were compared using the Chi-square test, and numerical variables using Student's T-test; p-values < 0.05 were considered significant.

The present study was approved by the Research Ethics Committee (REC) of the IPPMG, Federal University of Rio de Janeiro - UFRJ, under Certificate of Presentation for Ethical Appreciation (CAAE) No. 45439221.3.0000.5264.

RESULTS

A total of 51 patients were attended from 2019 to 2021. Group A included 32 patients: 60% (19/32) male and 47% (15/32) from the city of Rio de Janeiro. The age range varied from two to 205 months (median of 109 months), with 47% (15/32) adolescents and 53% (17/32) children. Group B comprised 19 patients: 58% (11/19) female and 84% (16/19) from the city of Rio de Janeiro. The age range varied from four to 182 months (median of 84 months), with 37% (7/19) adolescents and 63% (12/19) children.

Group A showed a 68% increase in the number of tuberculosis cases when compared to the previous year (group B). Both groups had a higher prevalence of children; however, group A had a higher frequency of adolescents than group B.

Figure 1 shows the number of new cases identified since the first case in group B, through the first case of COVID-19 in Brazil, the declaration of COVID-19 as a pandemic (3/11/2020), and the beginning and end of the lockdown (May to October 2020), up to

the implementation of new restrictive measures (3/26/2021).

As for the case outcomes, three patients died in group A, while none died in group B.

Figure 2 shows the forms of tuberculosis presentation in each group.

The data on clinical history, contact with tuberculosis patients, TST results, and healthcare prior to the final diagnosis in patients with PTB, EPTB, and PTB + EPTB in groups A and B are described in Table 1.

The radiological aspects of children and adolescents with PTB and PTB + EPTB were distributed in groups A and B. The three main forms observed were: expansile pneumonia, pleural effusion, and lymph node hilum enlargement. In group A, they represented 62% of the cases, with 28% (9/32) exhibiting expansile pneumonia, 25% (8/32) pleural effusion, and 9% (3/32) lymph node hilum enlargement. Meanwhile, in group B, they represented 84% of the cases, with 42% (8/19) with expansile pneumonia, 31% (6/19) pleural effusion, and 11% (2/19) lymph node hilum enlargement.

The 14 patients with PTB presented clinical scores equal to or greater than 30 points, with 100% of the patients in group A (6/6) and 87% in group B (7/8). The laboratory tests used are described in Table 2.

In group A, six patients showed detectable results in the Ultra test, while in group B, two showed detectable results in the Xpert test. In groups A and B, 33% (3/19) and 25% (8/32) of the patients, respectively, were diagnosed with tuberculosis and started treatment during hospitalization.

The types of EPTB in groups A and B are detailed in Table 3.

Coinfection with HIV was identified in 2/19 of the tested patients: one patient in group A (with severe

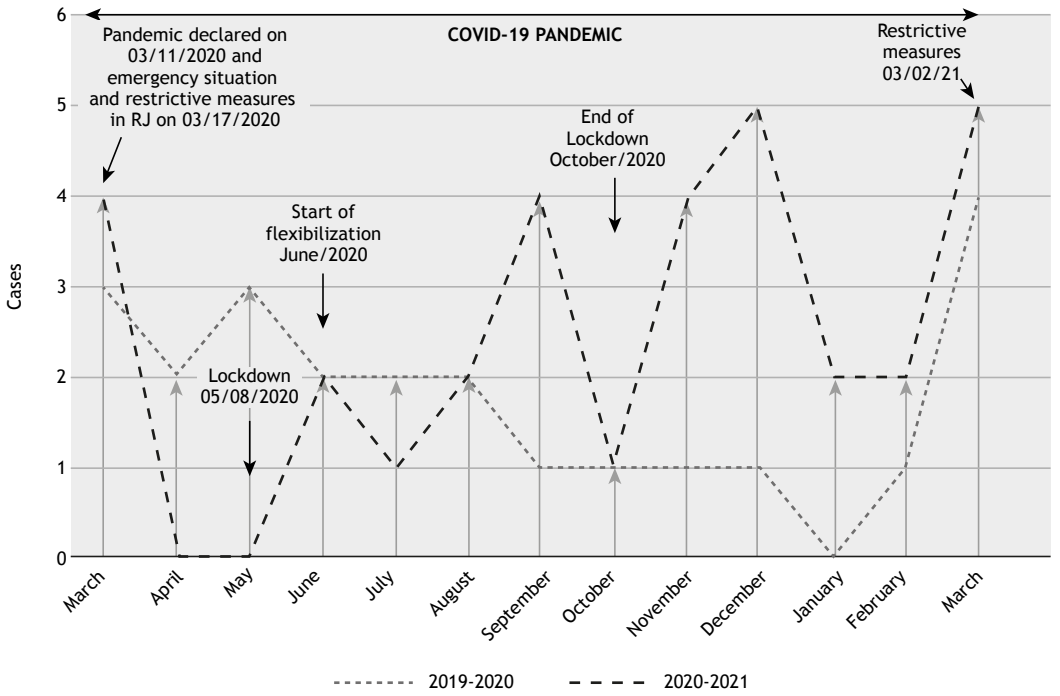

Figure 1. Graph indicating the number of active tuberculosis cases diagnosed at the IPPMG-UFRJ from 2019–2021.

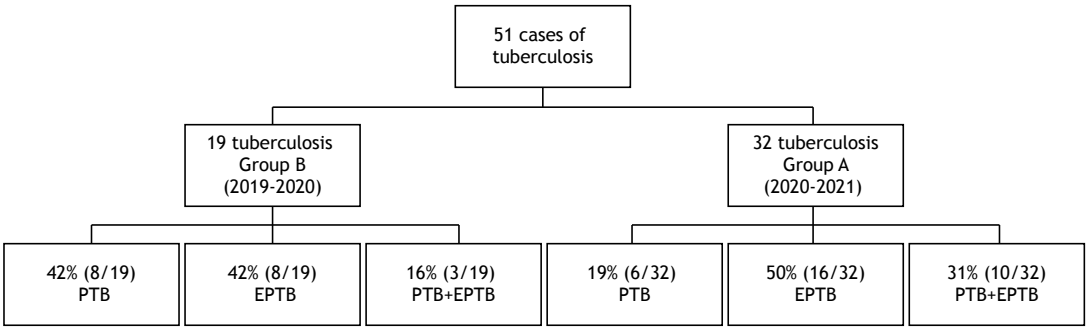

Figure 2. Flowchart of tuberculosis distribution by clinical presentation. EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis. Group A - 2020–2021; Group B - 2019–2020.

Table 1. Clinical data, diagnosis, and therapeutic course from 2019–2021.[a]

		TOTAL (n = 51)		PTB (n = 14)		EPTB (n = 24)		PTB + EPTB (n = 13)	
		Group							
		A (n = 32)	B (n = 19)	A (n = 6)	B (n = 8)	A (n = 16)	B (n = 8)	A (n = 10)	B (n = 3)
Clinical History	Fever	25 (78%)	13 (68%)	6 (100%)	5 (62%)	13 (81%)	5 (62%)	6 (60%)	3 (100%)
	Cough	10 (32%)	7 (37%)	5 (83%)	6 (75%)	1 (6%)	0 (0%)	4 (40%)	1 (33%)
	Weight loss	11 (35%)	6 (30%)	2 (33%)	5 (62%)	6 (40%)	0 (0%)	3 (30%)	1 (33%)
	Adynamia	11 (35%)	2 (10%)	2 (33%)	2 (25%)	7 (43%)	0 (0%)	3 (30%)	0 (0%)
	Adenomegaly	14 (45%)	7 (37%)	0 (0%)	0 (0%)	9 (60%)	7 (87%)	5 (50%)	0 (0%)
	Dyspnea	8 (25%)	5 (25%)	4 (66%)	1 (12%)	0 (0%)	3 (20%)	4 (40%)	3 (100%)
Prior Service Attention	Yes	20 (63%)	14 (73%)	3 (50%)	5 (62%)	10 (63%)	8 (100%)	7 (70%)	1 (34%)
Contact with Tuberculosis	Yes	11 (35%)	11 (58%)	1 (12%)	5 (62%)	6 (40%)	5 (45%)	4 (40%)	1 (33%)
	Group	A (n = 28)	B (n = 15)	A (n = 5)	B (n = 5)	A (n = 13)	B (n = 8)	A (n = 10)	B (n = 2)
Positive Tuberculin Test	Yes	16 (52%)	12 (63%)	2 (40%)	4 (80%)	7 (54%)	6 (75%)	7 (70%)	2 (100%)

EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis. Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%).

immunosuppression according to the Center for Disease Control and Prevention (CDC) classification)[13] and one patient in group B. Both had a previous diagnosis of HIV and were using antiretroviral therapy, but with poor adherence by the patient in group A. The graph in Figure 3 represents the time expended from symptom onset (days) until the final diagnosis of tuberculosis in groups A and B.

Group A presented greater variability than group B; this value dispersion resulted in a significant variation in the number of days since symptom onset. Outliers were found on different days in group A. The median number of days for the diagnosis of tuberculosis was 56 days in group A and 42 days in group B ($p < 0.01$).

DISCUSSION

The present study was conducted at a referral hospital in Rio de Janeiro (RJ), Brazil, and showed that the COVID-19 pandemic in Brazil led to delayed tuberculosis diagnoses in children and adolescents.

The COVID-19 pandemic reduced the demand for care at health centers. This, added to poverty and confinement in households where many people live together in small physical spaces, which are mostly poorly ventilated,[14] increased the number of tuberculosis cases in Brazil, an effect that was also identified at our service.

Our study shows that there were more tuberculosis cases in the first year of the pandemic than in the same period in the previous year, predominantly in children over five years of age, in both years. According to the World Health Organization, 11% of the children in the world had tuberculosis in 2020. With respect to adults, men were found to be more affected than women.[15] Although the age group was different, this pattern was observed herein in the patients from group A; however, the same did not occur in group B. As for clinical presentation, symptoms of fever and cough were more prevalent when evaluating PTB and combined cases, which contributed to the MoH-Brazil clinical score. Group B also presented low laboratory test (AFB and culture) positivity, corroborating the fact that children are paucibacillary or bacillus-negative. Nevertheless, with the replacement of the Gene Xpert MTB-RIF cartridge with the Ultra cartridge, in 2020, a greater number of patients in group A had their diagnosis of tuberculosis confirmed; this was due to the fact that the latter method increases the sensitivity of the diagnosis on account of its lower detection limit for M.tb.[12] The Ultra test has a detection limit of M.tb of less than 15.6 CFU, while the Xpert assay has a limit of 116 CFU. Despite the use of this new technique, considering the singularities of PTB in children and adolescents, MoH-Brazil recommends that the diagnosis in this age group be performed based on the scoring system. This system values clinical, radiological, and epidemiological data and does not include bacteriological confirmation.[11]

In group A, the EPTB cases showed a greater variety of sites affected by the disease, including rarer and more severe forms than in group B. The lack of access to healthcare services and the non-specificity of symptoms, which can be confused with other diseases, may have contributed to this finding.[6]

Likewise, the emergency care that was previously available and the greater delay in the diagnosis in group A can be attributed to the difficult immediate diagnosis in the period from 2020 to 2021 due to the greater demand for emergency services caused by the pandemic.[6]

Table 2. Laboratory characteristics of children and adolescents with tuberculosis in groups A and B.[a]

AFB	TOTAL (n = 43)		p-value*	PTB (n = 13)		p-value*	EPTB (n = 17)		p-value*	PTB + EPTB (n = 10)		p-value*
Group	A (n = 29)	B (n = 14)		A (n = 6)	B (n = 7)		A (n = 12)	B (n = 5)		A (n = 8)	B (n = 2)	
Positive	3 (9%)	4 (28%)	<0.17	2 (33%)	3 (43%)	<0.7	0 (0%)	0 (0%)	<0.8	1 (12%)	1 (50%)	<0.2
Negative	23 (91%)	10 (72%)		4 (67%)	4 (57%)		12 (100%)	5 (100%)		7 (88%)	1 (50%)	
Culture *M.tb.*	TOTAL (n = 31)			PTB (n = 11)			EPTB (n = 14)			PTB + EPTB (n = 6)		
Group	A (n = 21)	B (n = 10)		A (n = 5)	B (n = 6)		A (n = 11)	B (n = 3)		A (n = 5)	B (n = 1)	
Positive	3 (15%)	3 (30%)	<0.3	1 (6%)	2 (33%)	<0.6	0 (0%)	1 (33%)	<0.04	2 (40%)	0 (0%)	<0.5
Negative	18 (85%)	7 (70%)		4 (94%)	4 (67%)		11 (100%)	2 (67%)		3 (60%)	1 (100%)	
XPERT	TOTAL (n = 33)			PTB (n = 10)			EPTB (n = 15)			PTB + EPTB (n = 9)		
Group	A (n = 23)	B (n = 10)		A (n = 5)	B (n = 5)		A (n = 12)	B (n = 3)		A (n = 7)	B (n = 2)	
Detectable[+]	18 (77%)	3 (30%)	<0.01	4 (60%)	2 (40%)	<0.19	8 (67%)	0 (0%)	<0.03	6 (86%)	1 (50%)	<0.2
Not Detectable	6 (23%)	7 (70%)		1 (20%)	3 (60%)		4 (33%)	3 (100%)		1 (14%)	1 (50%)	

EPTB: extrapulmonary tuberculosis; PTB: pulmonary Tuberculosis; Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%). *Chi-square test. [+]In the Ultra test, the category trace was included as detectable.

The analysis of the time taken until the diagnosis of tuberculosis in group A, even with patients seeking emergency care, showed a greater number of previous visits and a longer time to establish the diagnosis in group A than in the previous year (group B). Thus, these patients may have had their access and clinical support for tuberculosis diagnosis affected by the interruption of tuberculosis services during the COVID-19 pandemic. Reduced tuberculosis diagnoses during the pandemic were observed worldwide, based on the lower number of notifications.[4]

In the context of tuberculosis-HIV coinfection, the number of cases found in this study was lower than 10%, corroborating what happens at the state level, in which the proportion of tuberculosis-HIV cases in the study period ranged from 7.9–8.6% of cases.[9] The only patient diagnosed during the pandemic had severe immunosuppression, which may have contributed to the unfavorable progression of the disease. Supposedly, this severity is due to the possible delay in seeking care and poor adherence, with partial or complete interruption of HIV control treatment, observed in the same period in the country and around the world, as occurred with the tuberculosis programs.[11]

It was not possible to identify the source of disease in most cases in group A; however, when identified, it was due to close contact with infected individuals. This finding may have been caused by the delayed diagnosis of active tuberculosis due to social isolation. Even though this protective measure helped reduce the spread of COVID-19, it has favored intra-household exposure to tuberculosis. Prolonged contact at the household level is one of the risk factors that increase active tuberculosis transmission.[15,16]

Our study showed a decrease in tuberculosis diagnoses in the first four months after the beginning of the pandemic, after the introduction of restrictive measures and lockdown, with no tuberculosis cases diagnosed in the two consecutive months. This may be justified by the reduced accessibility of patients to medical services due to interrupted or difficult access to public transport or canceled follow-up visits.[7] As a result of less restrictive measures, more than twice as many cases were recovered over the following months, peaking after the end of the lockdown period with four times more cases than at the beginning of the pandemic in the state of Rio de Janeiro.

More deaths were observed in group A, possibly as a result of restrictive measures and the increased time for diagnosis during the COVID-19 pandemic. In Rio de Janeiro, the mortality rate that had been decreasing up to 2017 has risen progressively since 2019, with the highest rate of 4.81 per 100,000 inhabitants in 2021. Thus, an increase of up to 20% in tuberculosis deaths can be expected in the next five years.[6,8,9]

This study had some limitations. The hospital where it was conducted is a reference center for

Table 3. Types of active EPTB from 2019–2021.[a]

Extrapulmonary forms	TOTAL (n = 37)		EPTB (n = 24)		PTB + EPTB (n = 13)	
Tuberculosis Group	A (n = 26)	B (n = 11)	A (n = 16)	B (n = 8)	A (n = 10)	B (n = 3)
Peripheral adenopathy	11 (42%)	5 (45%)	8 (52%)	5 (62%)	3 (30%)	0 (0%)
Pleural	5 (19%)	5 (45%)	1 (6%)	2 (25%)	4 (40%)	3 (100%)
Peritoneal	2 (7%)	1 (10%)	2 (12%)	1 (13%)	0 (0%)	0 (0%)
Meningitis	1 (4%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Bone	2 (8%)	0 (0%)	1 (6%)	0 (0%)	1 (10%)	0 (0%)
Cutaneous	1 (4%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)
Others *	4 (16%)	0 (0%)	2 (12%)	0 (0%)	2 (20%)	0 (0%)

CNS: central nervous system; EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis; Group A (2020–2021); Group B (2019–2020). [a]Values expressed as n (%). *Total of four patients: one with meningitis + ophthalmic tuberculosis; one with peritoneal + skin tuberculosis; one with pleural + ganglionic tuberculosis, and one with bone + pleural + pericardial tuberculosis.

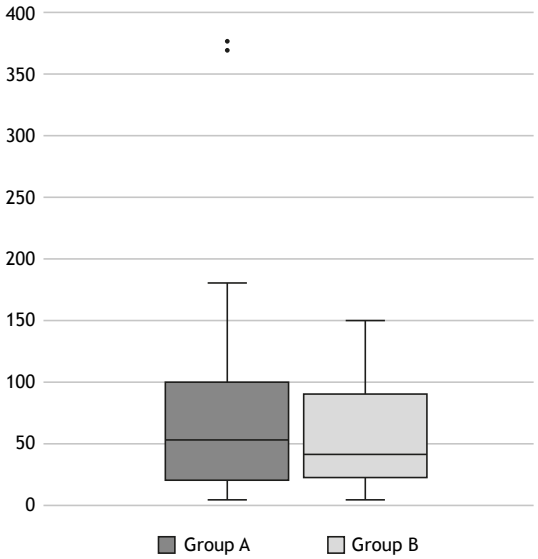

Figure 3. Box plot graph for the time variable for tuberculosis diagnosis in the period from 2019–2021.

tuberculosis, not necessarily reflecting what takes place in basic healthcare units, which are the centers for COVID-19 cases that are more accessible to the population.

The negative impact of the pandemic on tuberculosis programs will still promote repercussions on society for several years to come; therefore, there is an urgent need to adopt actions to mitigate and reverse this impact. The immediate priority is to restore access to and the provision of essential tuberculosis services without neglecting care for other diseases, including COVID-19 and AIDS.

AUTHOR CONTRIBUTIONS

Study design: MASP, RBA, AAAIP, CCS, MFBPS, ACCF, CBH, TFA, SF. Data collection: MASP. Data analysis: MASP, RBA, ACCF, CBH, TFA, CCS. Manuscript writing: MASP. Manuscript revision: RBA, ARF, AAAIP, ACCF, CBH, TFA, SF, MFBPS, CCS. Study supervision: CCS.

REFERENCES

1. Brazil. Ministry of Health. Department of Chronic Diseases and Sexually Transmitted Infections [homepage on the Internet] Brasília: the Ministry; [updated 2020 Mar 25; cited 2022 Feb 15]. Epidemiological Bulletin - Tuberculosis 2020. Available from: http://www.aids.gov.br/pt-br/pub/2020/boletim-epidemiologico-de-turbeculose-2020.
2. Brazil. Ministry of Health. Department of Chronic Diseases and Sexually Transmitted Infections. General Coordination of Surveillance of Chronic Respiratory Transmitted Diseases. [homepage on the Internet] Brasília: the Ministry; [updated 2019 Nov 28; cited 2022 Feb 15]. Overview of tuberculosis in Brazil: epidemiological and operational indicators. [Adobe Acrobat document, 76p]. Available from: http://www.aids.gov.br/pt-br/pub/2019/panorama-da-tuberculose-no-brasil-indicadores-epidemiologicos-e-operacionais.
3. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [updated 2020 Oct 14; cited 2022 Feb15]. Global tuberculosis report 2020. [Adobe Acrobat document, 232p]. Available from: https://www.who.int/publications/i/item/9789240013131.
4. World Health Organization. [homepage on the Internet]. Geneva: World Health Organization [updated 2021 Oct 14; cited 2022 Feb 15]. Global tuberculosis report 2021. [Adobe Acrobat document, 57p]. Available from: https://www.who.int/publications/i/item/9789240037021.
5. Portaldeboaspraticas.iff.fiocruz.br [homepage on the Internet] Rio de Janeiro: FIOCRUZ. National Institute of Health for Women, Children and Adolescents Fernandes Figueira. [updated 2020 Ago 11; cited 2022 Feb 15]. COVID-19 and Child and Adolescent Health. [Adobe Acrobat document, 70p]. Available from: https://portaldeboaspraticas.iff.fiocruz.br/atencao-crianca/covid-19-saude-crianca-e-adolescente/.
6. Silva DR, Mello FCQ, D'Ambrosio L, Centis R, Dalcolmo MP, Migliori GB. Tuberculosis and COVID-19, the new cursed duet: what differs between Brazil and Europe? J Bras Pneumol. 2021 Apr 30;47(2):e20210044. https://doi.org/10.36416/1806-3756/e20210044.
7. Migliori GB, Thong PM, Akkerman O, Alffenaar JW, Álvarez-Navascués F, Assao-Neino MM, et al. Worldwide Effects of Coronavirus Disease Pandemic on Tuberculosis Services. January-April 2020. J Emerg Infect Dis. 2020 Nov;26(11):2709-2712. https://doi.org/10.3201/eid2611.203163.
8. Maciel EL, Silva PEAD. Fighting tuberculosis: from 1993 to 2035 during the COVID-19 era. J Bras Pneumol. 2021 Apr 30:e20210033. https://doi.org/10.36416/1806-3756/e20210033.
9. Rio de Janeiro. Municipal Health Department. Undersecretariat of Promotion, Primary Care and Health Surveillance. [homepage on the Internet] Rio de Janeiro: the Ministry [updated 2022 Mar; cited 2022 Feb15]. Tuberculosis Epidemiological Bulletin in the city of Rio de Janeiro: perspective and challenges. [Adobe Acrobat document, 40p]. Available from: https://svs.rio.br/epirio/publicacoes/boletins/Boletim_Epidemiologico_Tuberculose%20no%20MRJ_31.03.2022.pdf.
10. Gie R. Diagnostic atlas of intrathoracic tuberculosis in children: A guide for low income countries. Paris: International Union Against

Tuberculosis and Lung Disease; 2003. 55p.

11. Brazil. Ministry of Health, Department of Health Surveillance. Department of Communicable Disease Surveillance. Manual of recommendations for tuberculosis control in Brazil. Brasília: Ministério da Saúde; 2019.
12. Aurilio RB, Ferreira S, Parente AAAI, Sant'Anna MFP, Pereira CS, Malaquias TDSS, et al. Gene-Xpert Ultra for the diagnosis of extrapulmonary tuberculosis in children and adolescents. Rev Inst Med Trop Sao Paulo. 2022 Feb 14;64:e12. https://doi.org/10.1590/S1678-9946202264012.
13. 1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age. Arch Dermatol. 1994 Dec;130(12):1485-86. https://doi.org/10.1001/archderm.1994.01690120017001.
14. Sociedade de Pediatria de São Paulo [homepage on the Internet]. São Paulo: Pediatra Atualize-se [updated 2020 Ago; cited 2022 February 15] Boletim – Coronavírus e a Pediatria [Adobe Acrobat document, 12p]. Available from: https://www.spsp.org.br/site/asp/boletins/AtualizeA5_Covid.pdf.
15. Alene KA, Wangdi K, Clements AC. Impact of the COVID-19 Pandemic on Tuberculosis Control: An Overview. Trop Med Infect Dis. 2020 Jul 24;5(3):123. https://doi.org/10.3390/tropicalmed5030123.
16. Martinez L, Lo NC, Cords O, Hill PC, Khan P, Hatherill M, et al. Paediatric tuberculosis transmission outside the household: challenging historical paradigms to inform future public health strategies. Lancet Respir Med. 2019 Jun;7(6):544-552. https://doi.org/10.1016/s2213-2600(19)30137-7.

J Bras Pneumol. 2022;48(6):e20220194
https://dx.doi.org/10.36416/1806-3756/e20220194

Persistence of symptoms and return to work after hospitalization for COVID-19

Helena Moraes Jardim de Azevedo[1,2], Nataly Winni Fernandes dos Santos[1,3], Mariana Lima Lafetá[3], André Luis Pereira de Albuquerque[4], Suzana Erico Tanni[5], Priscila Abreu Sperandio[3], Eloara Vieira Machado Ferreira[3]

1. Faculdades Metropolitanas Unidas, São Paulo (SP) Brasil.
2. Disciplina de Pneumologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, – EPM/Unifesp – São Paulo (SP) Brasil.
3. Setor de Função Pulmonar e Fisiologia Clínica do Exercício – SEFICE – Disciplina de Pneumologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, – EPM/Unifesp – São Paulo (SP) Brasil.
4. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
5. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

Submitted: 31 May 2022.
Accepted: 16 October 2022.

Study carried out at the Hospital São Paulo, Escola Paulista de Medicina, Universidade Federal de São Paulo, – EPM/Unifesp – São Paulo (SP) Brasil.

ABSTRACT

Many patients hospitalized with COVID-19 were unable to return to work or their return was delayed due to their health condition. The aim of this observational study was to evaluate the impact of moderate-to-severe and critical COVID-19 infection on persistence of symptoms and return to work after hospital discharge. In this study, two thirds of hospitalized patients with pulmonary involvement reported persistence of symptoms six months after COVID-19 infection, such as memory loss (45.5%), myalgia (43.9%), fatigue (39.4%), and dyspnea (25.8%), and 50% slowly returned to work, with repercussions due to fatigue and/or loss of energy.

Keywords: COVID-19/complications; COVID-19/rehabilitation; Return to work; Hospitalization; Survivors.

The new coronavirus disease (COVID-19) was declared a pandemic by the WHO in March of 2020. Since then, the disease has left millions of victims worldwide, accounting for more than 500 million confirmed cases and a lethality rate around 2% in the 2020-2021 period and 1.2% in 2022.[1] There has been a significant reduction in the number of severe cases and deaths after the start of vaccination; however, COVID-19 survivors may have persistent symptoms related to cardiopulmonary, neurological, and psychological sequelae, among others, for a long time.[2] The definition of this condition is still uncertain, but it has been acknowledged that persistence of symptoms longer than 12 weeks after acute infection has been called post-COVID syndrome (or long COVID) and has an important impact on quality of life and health status,[3-5] which may negatively influence activities of daily living and return to work, with consequences for these patients' mental health. Studies have shown that many patients were unable to fully or partially return to work, or their return was delayed due to their health condition.[4-7] The aim of this observational study was to evaluate the impact of moderate-to-severe and critical COVID-19 infection, based on the WHO severity classification, on sequelae symptoms and return to work after six months, as well as whether survivors performed any physical activities after hospital discharge, between the first and second waves of the pandemic in Brazil.

Ninety-six patients included in the FENIX study (ReBec no. RBR-8j9kqy) were referred to the post-COVID outpatient clinic of the Respiratory Division of the *Universidade Federal de São Paulo/Escola Paulista de Medicina*, located in the city of São Paulo, Brazil, after having been admitted to the Hospital São Paulo (the University hospital) with COVID-19 between May of 2020 and May of 2021, with a positive RT-PCR, lung impairment confirmed on chest CT scans, and need for oxygen supplementation, were invited to participate in the study. These patients were periodically evaluated at the outpatient clinic, as follows: 15 days after discharge and 3-6 months after the onset of COVID-19 symptoms. After this period, the patients were contacted by telephone 6-9 months after hospitalization and answered questions from a standardized questionnaire elaborated by the researchers to assess persistence of symptoms, time to symptom resolution, return to work, and presence of loss of energy or fatigue during work. The patients were also asked whether they performed any physical activity after discharge (outpatient rehabilitation, home rehabilitation, or independent physical activity). Data were

Correspondence to:
Eloara Vieira Machado Ferreira. Rua Botucatu, 740, 3º andar, Disciplina de Pneumologia, Vila Clementino, CEP 04039-002, São Paulo, SP, Brasil.
Tel.: 55 11 5576 4848 (VOIP 17305). E-mail: eloara.ferreira@unifesp.br
Financial support: None.

collected between the months of October and November of 2021. Of the 96 patients contacted by telephone, 71 completed the questionnaire.

In the sample of 71 patients, 62% were male, with a mean age of 52 years. The patients presented with two or more comorbidities and/or risk factors, mainly systemic hypertension (52%), former smoking (34%), obesity (27%), and diabetes mellitus (26%). More than half of patients had been admitted to the ICU. Prior to hospitalization, most of them had a job/occupation (Table 1).

In the first outpatient visit after hospital discharge, 70% of patients reported symptoms, mainly dyspnea, myalgia, and cough (Table 1). In the assessment carried out by questionnaire, most of the patients still had symptoms, notably memory loss, myalgia, fatigue, and dyspnea. Among the asymptomatic patients, 35% recovered within three months. Regarding work, 96.3% of patients reported that they had returned to work when they were interviewed, half of them had returned to work within the first 30 days. Among these patients, the majority reported feeling "less energy" or fatigue during the workday (Table 2).

During the first visit, patients who reported not to perform rehabilitation were referred to a rehabilitation center or were instructed to perform physical activity. Most patients (54/71) performed some type of physical activity after discharge and continued to do so (on average, 2-3 times a week) even by the time when they were interviewed (Table 2). Among asymptomatic patients, 90% had performed some type of physical activity in comparison with 45% of the patients that had persistent symptoms.

In our study, two thirds of the hospitalized patients with pulmonary involvement reported persistence of symptoms in the telephone interview, and return to work was slow in 50% of patients (more than 30 days after discharge) with symptoms such as feeling "loss of energy" and/or fatigue, or other complaints throughout the workday. The main symptoms reported by our patients were similar to those described in the literature.[5-7] Although the post-COVID syndrome has not fully been understood, the development of long COVID does not have a linear relationship with the severity of the disease during hospitalization or with being part of the elderly population; it may affect different age groups and even people who have had mild COVID-19 and may continue from weeks to years.[4,6,8,9] Regarding the proportion of survivors after hospitalization with at least one symptom after COVID-19, there was a significant reduction over time: 68% in 6 months and 49% in 12 months (p <

Table 1. Demographics and baseline characteristics of patients during hospitalization for COVID-19.[a]

Characteristic	(n = 71/96)[b]
Demographic/anthropometric	
Age, years	52 ± 13
Male gender	44 (62)
BMI, kg/m^2	30.0 ± 4.5
Comorbidities/risk factors[c]	
≥ 2	46 (64.8)
Length of stay, days	
Hospital	12 [7-18]
ICU	10 [5-15]
Oxygen supplementation	
Ward (via nasal cannula or mask)	30 (42.3)
ICU (HFNC, NIV, or MV)	41 (57.7)
MV	18 (43.9)
Work status before COVID-19	
Have a job/occupation	54 (76.0)
Homemaker	7 (9.9)
Retired	3 (4.2)
Unemployed	7 (9.9)
Symptoms related after discharge (1st medical appointment)	
Dyspnea	38 (53.5)
Myalgia	15 (21.1)
Cough	12 (16.9)
Fatigue	4 (5.6)
Chest pain	3 (4.2)
Dysgeusia	2 (2.8)

HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; and MV: mechanical ventilation. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]No significant differences were found between the sample of patients who completed the survey questionnaire or not (n = 71 vs. n = 25; data not shown). [c]Systemic hypertension, former smoking, obesity, diabetes, hyperlipidemia, asthma, chronic kidney disease, psychiatric disease, kidney transplant.

Table 2. Results from the research survey questionnaire applied between six and nine months after hospital discharge.[a]

Survey Questionnaire	(n = 71)
Part I: Persistence of symptoms	
1. Do you still have symptoms? (YES)	51 (71.8)
2. What symptoms have persisted?	
Memory loss	30 (58.8)
Myalgia/Arthralgia	29 (56.8)
Fatigue	26 (50.9)
Dyspnea	17 (33.3)
Insomnia	14 (27.4)
Depressed mood	12 (23.5)
Headache	12 (23.5)
Sensory deficit	11 (21.5)
Chest pain	10 (19.6)
Cough	8 (15.6)
Other[b]	< 5
3. How long did you become asymptomatic after hospital discharge?[c]	
Up to 3 months	7 (35)
3 to 6 months	5 (25)
More than 6 months	5 (25)
I do not remember	3 (15)
Part II: Return to work[d]	
1. Did you return to work after COVID-19? (YES)	52 (96.3)
2. How long after discharge were you able to return to your job?	
Up to 1 month	28 (53.8)
1 to 3 months	12 (23.1)
3 to 6 months	7 (13.5)
More than 6 months	5 (9.6)
3. After returning to work, did you feel less energy or fatigue throughout the day? (YES)	38 (73.0)
Part III: Physical activity after COVID-19	
1. Have you performed any physical activities after discharge? (YES)	43 (60.6)
2. What kind of activities have you performed in post-COVID?	
Outpatient rehabilitation	18 (41.9)
Home rehabilitation	15 (34.9)
Independent physical activity	10 (23.3)
2. How often have you performed the activities?	
Once a week	10 (23.2)
Twice a week	11 (25.5)
Three or more times a week	22 (51.1)
3. Do you still practice any physical activity? (YES)	33 (76.7)

[a]Values expressed as n (%). [b]Hair/nail loss, sexual dysfunction, dizziness/malaise, dysgeusia, or inappetence. [c]n = 20. [d]n = 54.

0.0001).[10] However, despite the improvement, there is still a high rate of persistence of symptoms in the long term, fatigue and muscle weakness being the most frequent ones. It is worth noting in our study that dyspnea was the most prevalent symptom (53.5%) after discharge, and few patients reported the presence of fatigue (5.6%). In the telephone interview, 50.9% of patients reported fatigue, but dyspnea complaints decreased to 33.3%. This may be due to the improvement of pulmonary sequelae, with recovery of lung function (improved dyspnea); however, a progressive increase in performing activities of daily living might have led to a greater perception of fatigue when compared with the period immediately after discharge.

Regarding the patients with a job/occupation, 96.3% reported having returned to work in the telephone interview, and 53.8% did it within 30 days. However, despite their return to work, most patients reported loss of energy and/or fatigue during the workday. In a study evaluating COVID-19 survivors at three months after hospital discharge, only 1 in 3 patients had returned to unrestricted work duty, more than one third of patients (34%) reported difficulty in performing basic activities of daily living, and most required physical therapy, occupational therapy, or brain rehabilitation.[7] This difference in the proportion of people who returned to work within the first 30 days may be due to the profile of the population included in that study.[7] It is important to consider that the

patients in our study came from the public health care system, who, in general, has a lower monthly income when compared with those who have access to the private health care system. This fact could have influenced the time to return to work even with the persistence of symptoms. In a study involving a cohort of COVID-19 survivors in China, 88% had returned to work at the 12-month follow-up visit; however, 24% were unable to return to the pre-COVID-19 level of work.[10] Persistent symptoms after returning to work may result in reduced overall well-being, difficulty in performing tasks that were previously performed, loss of concentration, and loss of work performance, in addition to economic and social impacts, which has been the subject of ongoing observational studies.[11] Evaluating the global impact of COVID-19 on life expectancy, as measured in disability-adjusted life-years, in which years of life lost and years of life lost to disability are assessed, economic losses per year of life were shown to be greater in South America than in North America.[12]

It has already been well established that rehabilitation accelerates the recovery of hospitalized patients after COVID-19. Seventy-seven percent of the included patients performed some type of physical activity and maintained training for an average of at least three months after discharge, and most performed exercises outside a rehabilitation center. Among the patients who remained asymptomatic, most performed some physical activity after discharge in comparison with the symptomatic group. A follow-up study of 299 patients hospitalized between March and May of 2020 showed that only 31% were referred for rehabilitation.[13] This may have been due to the limited availability of rehabilitation centers during the first wave and the lack of implementation, at that time, of home rehabilitation care and/or telerehabilitation by recruitment of health care providers to inpatient care. Among patients who were referred for rehabilitation, there was improvement in quality of life, as assessed with the Medical Outcomes Study 36-item Short-Form Health Survey, when compared with patients who did not undergo rehabilitation.[13] The goal of post-COVID rehabilitation is to improve prolonged symptoms and regain functionality, avoiding the complications associated with the disease by prescribing individualized physical training. Early interventions have been related to better disease recovery and quality of life.[14] Home rehabilitation expands the number of patients that can be treated after hospital discharge and, according to the evidence found so far, improvement of persistent symptoms such as fatigue and dyspnea can directly influence the return to activities.[15]

As limitations of the study, we can cite the small sample size and the observational follow-up design. Indication of rehabilitation was at the discretion of the patient's health care team. Moreover, no details were collected regarding the patients' job/occupation or their socioeconomic level to assess the impact of restrictions after the return to work and/or absenteeism related to the presence of persistent symptoms.

In summary, after hospital discharge of moderate-to-severe or critical COVID-19 patients, although most patients returned to work, approximately 70% still had symptoms related to long COVID between six and nine months after the infection, which could impact on their daily work performance. More than half of the patients performed some type of physical activity. Future studies are needed to assess the real impact of persistence of symptoms, rehabilitation, and unrestricted return to work.

AUTHOR CONTRIBUTIONS

All authors contributed to all stages of this study, including study conception and design, data acquisition, analysis, and interpretation, preparation and revision of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Johns Hopkins University [homepage on the Internet]. Baltimore (MD): the University; c2022 [cited 2022 Apr 26]. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE). Available from: https://coronavirus.jhu.edu/map.html
2. Cassar MP, Tunnicliffe EM, Petousi N, Lewandowski AJ, Xie C, Mahmod M, et al. Symptom Persistence Despite Improvement in Cardiopulmonary Health - Insights from longitudinal CMR, CPET and lung function testing post-COVID-19. EClinicalMedicine. 2021;41:101159. https://doi.org/10.1016/j.eclinm.2021.101159
3. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021;93(2):1013-1022. https://doi.org/10.1002/jmv.26368
4. Bouteleux B, Henrot P, Ernst R, Grassion L, Raherison-Semjen C, Beaufils F, et al. Respiratory rehabilitation for Covid-19 related persistent dyspnoea: A one-year experience. Respir Med. 2021;189:106648. https://doi.org/10.1016/j.rmed.2021.106648
5. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38:101019. https://doi.org/10.1016/j.eclinm.2021.101019
6. Sanchez-Ramirez DC, Normand K, Zhaoyun Y, Torres-Castro R. Long-Term Impact of COVID-19: A Systematic Review of the Literature and Meta-Analysis. Biomedicines. 2021;9(8):900. https://doi.org/10.3390/biomedicines9080900
7. Vanichkachorn G, Newcomb R, Cowl CT, Murad MH, Breeher L, Miller S, et al. Post-COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort. Mayo Clin Proc. 2021;96(7):1782-1791. https://doi.org/10.1016/j.mayocp.2021.04.024
8. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53(10):737-754. https://doi.org/10.1080/23744235.2021.1924397
9. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 Symptom Burden: What is Long-COVID

and How Should We Manage It?. Lung. 2021;199(2):113-119. https://doi.org/10.1007/s00408-021-00423-z

10. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study [published correction appears in Lancet. 2022 May 7;399(10337):1778]. *Lancet*. 2021;398(10302):747-758. https://doi.org/10.1016/S0140-6736(21)01755-4
11. Declercq PL, Fournel I, Demeyere M, Ksiazek E, Meunier-Beillard N, Rivière A, et al. Influence of socioeconomic status on functional recovery after ARDS caused by SARS-CoV-2: a multicentre, observational study. BMJ Open. 2022;12(4):e057368. https://doi.org/10.1136/bmjopen-2021-057368
12. Fan CY, Fann JC, Yang MC, Lin TY, Chen HH, Liu JT, et al. Estimating global burden of COVID-19 with disability-adjusted life years and value of statistical life metrics. J Formos Med Assoc. 2021;120 Suppl 1:S106-S117. https://doi.org/10.1016/j.jfma.2021.05.019
13. Lorent N, Vande Weygaerde Y, Claeys E, Guler Caamano Fajardo I, De Vos N, De Wever W, et al. Prospective longitudinal evaluation of hospitalised COVID-19 survivors 3 and 12 months after discharge. ERJ Open Res. 2022;8(2):00004-2022. https://doi.org/10.1183/23120541.00004-2022
14. Udina C, Ars J, Morandi A, Vilaró J, Cáceres C, Inzitari M. Rehabilitation in adult post-COVID-19 patients in post-acute care with Therapeutic Exercise. J Frailty Aging. 2021;10(3):297-300. https://doi.org/10.14283/jfa.2021.1
15. Frutos-Reoyo EJ, Cantalapiedra-Puentes E, González-Rebollo AM. Home rehabilitation in patients with COVID-19 [Article in Spanish]. Rehabilitacion (Madr). 2021;55(2):83-85. https://doi.org/10.1016/j.rh.2020.10.004

J Bras Pneumol. 2022;48(6):e20220270
https://dx.doi.org/10.36416/1806-3756/e20220270

Environmental impact of inhaler devices on respiratory care: a narrative review

Marilyn Urrutia-Pereira[1], Herberto José Chong-Neto[2], Tonya A Winders[3], Dirceu Solé[4]

1. Departamento de Medicina, Universidade Federal do Pampa, Uruguaiana (RS) Brasil.
2. Departamento de Pediatria, Universidade Federal do Paraná, Curitiba (PR) Brasil.
3. Global Allergy and Airways Patient Platform, Vienna, Austria.
4. Departamento de Pediatria, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo (SP) Brasil.

Submitted: 19 July 2022.
Accepted: 7 November 2022.

ABSTRACT

Climate change is a huge and present threat to human health. This article aims to deepen the knowledge about the environmental impact of inhaler devices on their carbon footprint for patients and health professionals, providing information that allows a better choice of the type of device to be prescribed for the treatment of asthma and COPD. This narrative and nonsystematic review was carried out by searching databases (PubMed, Google Scholar, SciELO, and EMBASE) for articles published between 2017 and 2022, written in Portuguese or in English, using the search words "inhalation device" OR "environmental." The review showed that global warming cannot be addressed by focusing only on inhaler devices. However, the devices that we use to treat respiratory diseases such as asthma and COPD, which are diseases that are aggravated by climate change, are also causing that change. Therefore, health professionals, patient organizations, and industries should take a lead in health policies to offer affordable alternatives to inhalers containing hydrofluoroalkane.

Keywords: Asthma; Pulmonary disease, chronic obstructive; Environmental health; Nebulizers and vaporizers.

INTRODUCTION

Climate change is a huge and present threat to human health. It disproportionately affects the poorest and most vulnerable individuals, including those with pre-existing lung diseases. The emission of greenhouse gases (GHG) plays a significant role in the genesis of climate change. Actions to minimize it must be carried out to protect current and future generations from its worst effects.[1]

As a result of these actions, governments worldwide have committed to legislative changes to reduce GHG emissions.[2] Although the efficacy and safety of medical treatments are always a priority, the health sector has significantly contributed to the increase in GHG emissions. In recent years, the environmental impacts arising from all aspects of life have become an increasingly unavoidable condition, and inhalation therapies are no exception.[3]

Asthma and COPD are the most common chronic respiratory diseases and are among the leading causes of morbidity and mortality worldwide.[4] It is estimated that there are at least 300 million patients with asthma and 328 million patients with COPD.[5]

Inhalation is the preferred route for the treatment of asthma and COPD. For that, inhalers are used, which are devices that reduce the morbidity and mortality associated with both diseases and significantly improve the quality of life of patients.[6,7] Global initiatives advocate the gradual reduction of inhaler devices that use fluorinated gas as a propellant—pressurized metered-dose inhalers (pMDI)—since such devices are associated with significant environmental impacts.[8]

Three main classes of inhalation therapy devices are available for patients with asthma and COPD: pMDIs, dry powder inhalers (DPIs), and soft mist inhalers (SMIs).[9] The carbon footprint of these inhaler devices is distinct, being more intense with pMDIs in comparison with DPIs and SMIs. That means that new approaches must be considered to balance environmental goals with patient health and well-being, maintaining a diverse range of therapeutic options for patients and physicians.[10]

This article aims to deepen the knowledge about the environmental impact of inhaler devices on their carbon footprint for patients and health professionals, providing information that allows a better choice of the type of device to be prescribed in the treatment of asthma and COPD patients, aiming to reduce their environmental impact. It also aims to inform policymakers who wish to reduce the carbon footprint in health systems.

INHALER DEVICES

pMDIs

Until the early 1990s, pMDIs that contained chlorofluorocarbon (CFC) as propellants were the most common way to administer inhalation therapy to patients with asthma and/or COPD. In 1987, the Montreal Protocol,[11] which focused on substances capable of destroying the ozone layer, recommended the progressive elimination of CFCs because it not only

Correspondence to:
Herberto José Chong-Neto. Rua Padre Camargo, 453, Alto da Glória, CEP 82540-220, Curitiba, PR, Brasil.
Tel.: 55 41 3208-6500. E-mail: h.chong@uol.com.br
Financial support: None.

ISSN 1806-3756

destroys the ozone layer but also has the potential to contribute to the already extremely high global warming.[12] Since then, new forms of inhalation therapy have been developed for patients with asthma and/or COPD.[13,14] In Brazil, such as in all countries that complied with the Montreal Protocol, we only use hydrofluoroalkane (HFA) as a propeller for pMDIs.

The global warming potential (GWP) of gases indicates how much warming a gas causes over a given period (typically 100 years) in comparison with CO_2, which was defined as GWP = 1; therefore, all other gases have higher values.[15,16]

CFC used to be the propellant for pMDIs, and, more recently, HFA has been introduced. The GWP of HFA is significantly higher due to its composition: HFC-134a and HFC-227ea, whose GWP are 1,300 and 3,350, respectively.[6]

MDIs commonly prescribed for chronic respiratory diseases contain hydrofluorocarbons (HFCs), which are powerful greenhouse gases and a significant cause of climate change. HFCs in MDIs (HFC-134a and HFC-227ea) are 1,000-3,000 times more potent than CO_2 and persist in the atmosphere for 14 years, causing climatic feedbacks. Currently, HFC-152a is a developing propellant that has a lower GWP when compared with the existing ones. Its launch is scheduled for 2025. However, according to the Kigali Amendment to the Montreal Protocol,[11] HFC-134a, HFC-227ea, and HFC-152a are expected to be phased out between 2020 and 2050. However, countries are free to choose how to phase out these HFCs during that period.

It is assumed that resulting from the high GWP values of HFC-134a and HFC-227ea, the use of HFCs in pMDIs accounted for direct emissions of approximately 18,000 $ktCO_2eq$ in 2018, representing approximately 0.03% of total global GHG emissions in that year.[17] In terms of CO_2eq emissions, a single dose of two jets of an HFC-134a pMDI is comparable to day-to-day activities emissions, such as traveling two kilometers on a Seat Ibiza Ecomotive car.[18,19]

DPIs

DPIs are devices that provide powdered medication (active ingredient mixed with excipients) without the need for a propellant gas. They are safe and effective for most patients, do not contain GHG, and are activated by forced patient inspiration. Thus, their life cycle assessments are substantially lower than those for pMDIs.[16,20]

Real-world evidence shows that the combined administration of inhaled corticosteroids and long-acting β_2 agonists in a single daily dose using a DPI can improve asthma control and adherence to treatment and can reduce the carbon footprint resulting from medical care. In addition to simplifying therapy, it improves asthma control and reduces GHG emissions. If we focus on patients with partially controlled or uncontrolled asthma, who might use large amounts of short-acting β_2 agonists (SABA) via a pMDI, instead of prioritizing inhaled corticosteroids via DPIs, there will be golden opportunities to make asthma treatment more effective, safe, and environmentally friendly.[21]

Patients who switched from pMDI-based maintenance therapy to DPI-based maintenance therapy more than halved their inhaler carbon footprint with no loss of asthma control. The inhaler's remaining carbon footprint can be reduced by switching from pMDI to DPI rescue medications or alternative lower carbon footprint rescue inhalers, if available.[22]

GHG emissions from asthma exacerbation management were highest for severe/life-threatening events, followed by moderate exacerbations. Treatment to reduce the severity and occurrence of exacerbations, such as effective, long-term control therapy using low emitting DPIs can help mitigate asthma care emissions. For mild exacerbations, the use of DPIs can eliminate associated emissions.[23]

In addition to a lower global warming potential, DPIs have additional benefits over pMDIs in other domains and should be considered as first-line therapy when clinically appropriate.[24]

SMIs

SMIs are small portable devices that produce aerosols of breathable diameter from aqueous formulations. These new-generation devices produce an aerosol by mechanisms other than those described for nebulizers. They consist of the collision of two jets of liquid to produce an aerosol, force the liquid through tiny holes with micron diameters, or use a mesh/vibrating plate or other new mechanisms (e.g., electrohydrodynamic effects). The improved efficiency and smaller aerosol particle size provided by these devices ensure that the aerosol generated is deposited deep into the lungs. SMIs are currently more expensive than standard pMDIs and DPIs.[3]

Nebulizers can also be used—although this typically occurs in an emergency setting or in cases when patients cannot use pMDIs or DPIs because they have physical or cognitive impairments or in patients who are at risk of having severe symptoms/exacerbations.[6]

It is difficult to make accurate comparisons among studies on the relative carbon footprint of inhalers due to the different methodologies employed. However, in general, all DPIs and SMIs have a substantially smaller carbon footprint than do pMDIs. Other environmental benefits may come from reusable inhalers and longer treatment packages (e.g., 90-day options instead of 30-day inhalers).

RECYCLING

Currently, less than 1% of inhaler devices are recycled every year. Their recycling has the potential to eliminate all emissions associated with their disposal; however, it is mandatory to recycle between 81% and 87% of the inhaler devices currently in use.[16] In clinical practice, such end-of-life recycling rates

can be very difficult to achieve and require significant investment and behavioral changes; nevertheless, if recycling schemes were launched now, they would achieve reductions in the short term.[9]

Recycling inhalers at specific locations such as pharmacies, as opposed to landfill disposal, should enable the reuse of plastic or aluminum components and reduce CO_2 emission.[21]

Improper disposal of pMDI devices with unused doses is especially worrying, because it not only increases the prescription load, but disused devices continue to release GHG, which persist in the atmosphere for up to 50 years.[9,17]

In a position statement on environment and lung health,[21] the British Thoracic Society has highlighted the importance of informing patients about how to avoid disposing of inhalers in landfills with the following recommendations:

- Expansion of recycling and disposal schemes to prevent remaining propellant gases from being released into the atmosphere and avoid waste of plastic packaging, and
- Information on where recycling and disposal schemes are available, including which major local pharmacy chains would offer the service.

MEDICAL CARE

The health sector needs to reduce GHG emissions to help mitigate climate change.[25] For that, proven and medically safe ecological alternatives are needed.[26] Indeed, the medication chosen must be appropriate for each patient. The final choice of the inhaler device must comply with different factors, such as the real efficacy of the molecules, factors related to patient use, cost, patient preference, "custom and practice" of the physician, clinical evaluation, appropriate education, and evaluation programs to ensure the correct technique for inhaler use.[21] Patient choice can also be improved by increasing the diffusion of publicly available information on the environmental impact of different inhalation products.[2,14,27,28]

Pepper et al.[29] warned that there is evidence that the short-term exposure to ozone may cause morbidity in individuals with asthma and suggested that exposures to levels below the currently allowed standard[30] may be associated with an increased use of SABA.

In an interview with inhaler prescribers, Walpole et al.[31] reported that only 9% discuss the environmental impact of inhalers with patients, and only 13% discuss the disposal of inhalers. However, 46% of the respondents said they would educate patients about the environmental impacts of inhalers.

Although some practical (dis)advantages of pMDIs and DPIs are known, it should be noted that[20]:

- The global warming effect of pMDIs is mainly caused by their use (95-98%), not by the manufacture of this class of inhaler devices.
- Unknown amounts of propellant gases may remain in the canister after use and, in variable time, will be released into the atmosphere.
- Most pMDIs do not have dose counters.
- Without a dose counter, it can be difficult to know how many doses are left in the device.
- Inadvertent use of empty pMDIs can lead to preventable exacerbations or even avoidable hospital admissions.
- Inadvertent replacement of a pMDI that still contains medications would incur unnecessary costs.
- Adherence to inhalation instructions can be problematic when changing devices, because not every patient uses a pMDI with the recommended spacer.
- Switching to a DPI can improve adherence to guidelines because spacer use is not required.
- Changes without sufficient education can result in lack of control of the disease, exacerbations, and increased use of health services.

CURRENT SITUATION

SABA via pMDIs accounts for a considerable share of the total inhaler market. They are cheaper than DPIs, and their overuse is common in many countries. Recent studies have shown that most of all SABA inhalers for asthma were prescribed to patients who were likely to use them excessively (≥ 3 inhalers prescribed per year).[32,33]

In Brazil, the real situation regarding the use of inhaler devices is not completely known. Table 1 shows the numbers of devices marketed from 2017 to 2021 according to therapeutic agents and devices. As we can see, there was an increase in sales during the period. It is worth highlighting the decrease in SABA sales during 2021,[34] a year that coincided with the

Table 1. Medications and inhaler devices (in units) used in the treatment of asthma and marketed in Brazil.

Medication/ID	Year[a]				
	2017	2018	2019	2020	2021
SABA/pMDI	6,659,604	8,734,188	8,913,888	9,071,179	7,767,193
LAMA/SMI	956,267	1,078,453	1,252,303	1,507,886	1,539,340
IC+LABA/pMDI (HFA propellant)	995,709	1,086,145	1,164,031	1,337,000	1,564,198
IC+LABA/DPI	7,765,098	7,764,689	8,627,569	9,561,575	10,004,885

Based on Walpole et al.[31] ID: inhaler device; SABA: short-acting β_2 agonists; pMDI: pressurized metered-dose inhaler; LAMA: long-acting muscarinic antagonists; SMI: soft mist inhaler; IC: inhaled corticosteroids; LABA: long-acting β_2 agonists; HFA: hydrofluoroalkane; and DPI: dry powder inhaler. [a]The period between July 1 and June 30 of the following year.

peak of the COVID-19 pandemic, when social isolation was more effective.[35]

A recently published alert has indicated how much CO_2 equivalent is released (carbon footprint) by activating inhaler devices per pharmacological agent[36] (Table 2).

COMPARISON TABLES OF CARBON FOOTPRINT

Data on the actual carbon footprint of individual inhalers are very limited; therefore, the following tables provide indicative rather than actual values. The carbon footprint for comparisons estimated that a typical car's average trip (9 land miles) produces 2,610 gCO_2eq (or 290 gCO_2eq per mile). The numbers are based on the mean CO_2eq values per inhaler as estimated by PrescQIPP.[37] The U.S. Environmental Protection Agency estimated that, in 2020, the discharge and leakage of HFA-containing pMDIs were responsible for generating 2.5 million metric tons of CO_2eq, the approximate equivalent to the emissions of 550,000 passenger vehicles driven for a year.[38] More objectively, the city of Uruguaiana, at the border between Brazil and Uruguay in the southern region of the country, has a public health care program for patients with asthma that quantitatively calculated the dispensation of SABA via pMDIs in one year (Table 3); therefore, we can have a picture of such a reality.

FINAL CONSIDERATIONS

The latest International Panel on Climate Change report[38] called for "urgent action to keep the global average temperature rise below 1.5°C," halting the destruction of nature. However, there remains an uncomfortable recognition that the provision of health services has contributed to global warming.[39]

Global warming cannot be addressed by focusing only on inhaler devices. However, the drugs that we use to treat respiratory diseases such as asthma and COPD, which are diseases that are aggravated by climate change, are also causing climate change.[27]

From the point of view of the industry and government, several pharmaceutical companies and national health organizations have developed 'Net Zero' commitments to achieving zero carbon emissions in their operations.[37] For companies that manufacture current HFC-containing pMDIs, they may represent a substantial proportion of the entire carbon footprint of the company.[3,40-44] More recently, published figures indicate that the use of pMDIs accounts for 13% and 36%, respectively, of AstraZeneca's and GSK's total carbon emissions.[45,46] Pharmaceutical companies should consider these issues in their strategic planning for new developments in inhalation therapy, such as reusable inhalers or longer treatment packages (e.g., 90-day rather than 30-day options),[47] so that they could reduce their carbon footprint.[3]

In conclusion, as long as we can offer safe and effective treatment to our patients, we cannot simply ignore the environmental aggression that other treatments can cause. Professional and patient organizations should take the lead in health policies to offer affordable alternatives to inhalers containing HFA. Following efficacy and safety considerations, comprehensive data on the carbon footprint of inhalation therapies will enable patients and their caregivers to make informed decisions about inhalation treatment. Pharmaceutical companies should consider these issues in their strategic planning for new developments in inhalation therapy. Hospital and health plan forms should also consider the environmental risks of inhaler propellants and prioritize options not containing HFA.

Responding to the threat of climate change will require innovation, leadership, and a broad perspective, but action is crucial if we are to protect the health of our patients.

AUTHOR CONTRIBUTIONS

All authors participated in the drafting and revision of the manuscript, as well as in the approval of the final version.

CONFLICTS OF INTEREST

None declared.

Table 2. Amount of CO_2 equivalent released per puff [CO_2eq/puff (g)] according to the pharmacological agent and device.

Product	CO_2eq/puff (g)
SABA (albuterol)[a]	60.4
LAMA DPI	18.75
LAMA SMI	13.0
IC+LABA DPI	18.75
IC+LABA pMDI	163.5

Based on Cabrera et al.[33] and IQVIA Brasil.[34] SABA: short-acting β_2 agonists; LAMA: long-acting muscarinic antagonists; DPI: dry powder inhaler; SMI: soft mist inhaler; IC: inhaled corticosteroids; and pMDI: pressurized metered-dose inhaler. [a]Hydrofluoroalkane propellant.

Table 3. Dispensation of short-acting β_2 agonists via pressurized metered-dose inhaler in the city of Uruguaiana, Brazil.

Year[a]	Assisted patients	pMDI, n	Puffs, n	CO_2eq (kg)
2018	848	1,446	289,200	1,746.8
2019	1,313	2,459	491,800	2,970.5
2020	933	2,231	446,200	2,695.0
2021	1,276	2,761	552,200	3,335.3

[a]From January 1 to December 31.

REFERENCES

1. Wilkinson AJK, Braggins R, Steinbach I, Smith J. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. BMJ Open. 2019;9(10):e028763. https://doi.org/10.1136/bmjopen-2018-028763
2. Starup-Hansen J, Dunne H, Sadler J, Jones A, Okorie M. Climate change in healthcare: Exploring the potential role of inhaler prescribing. Pharmacol Res Perspect. 2020;8(6):e00675. https://doi.org/10.1002/prp2.675
3. Woodcock A, Beeh KM, Sagara H, Aumônier S, Addo-Yobo E, Khan J, et al. The environmental impact of inhaled therapy: making informed treatment choices. Eur Respir J. 2022;60(1):2102106. https://doi.org/10.1183/13993003.02106-2021
4. Global Initiative for Asthma (GINA) [homepage on the Internet]. Bethesda: GINA; c2022 [cited 2022 May 1]. Global Strategy for Asthma Management and Prevention (Updated 2022). [Adobe Acrobat document, 225p.]. Available from: https://ginasthma.org/wp-content/uploads/2022/05/GINA-Main-Report-2022-FINAL-22-05-03-WMS.pdf
5. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2022 Apr 1]. 2020 Global Strategy for Prevention, Diagnosis and Management of COPD: 2022 Report. Available from: https://goldcopd.org/2022-gold-reports-2/
6. Usmani OS. Choosing the right inhaler for your asthma or COPD patient. Ther Clin Risk Manag. 2019;15:461-472. https://doi.org/10.2147/TCRM.S160365
7. Usmani OS, Scullion J, Keeley D. Our planet or our patients-is the sky the limit for inhaler choice?. Lancet Respir Med. 2019;7(1):11-13. https://doi.org/10.1016/S2213-2600(18)30497-1
8. Attar-Zadeh D, Lewis H, Orlovic M. Health-care Resource Requirements and Potential Financial Consequences of an Environmentally Driven Switch in Respiratory Inhaler Use in England. J Health Econ Outcomes Res. 2021;8(2):46-54. https://doi.org/10.36469/jheor.2021.26113
9. Pernigotti D, Stonham C, Panigone S, Sandri F, Ferri R, Unal Y, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ Open Respir Res. 2021;8(1):e001071. https://doi.org/10.1136/bmjresp-2021-001071
10. Panigone S, Sandri F, Ferri R, Volpato A, Nudo E, Nicolini G. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. BMJ Open Respir Res. 2020;7(1):e000571. https://doi.org/10.1136/bmjresp-2020-000571
11. UN Environment Programme [homepage on the Internet]. Nairobi: UN Environment Programme; [cited 2022 Apr 1]. The Montreal Protocol. Available from: https://www.unep.org/ozonaction/who-we-are/about-montreal-protocol
12. Young PJ, Harper AB, Huntingford C, Paul ND, Morgenstern O, Newman PA, et al. The Montreal Protocol protects the terrestrial carbon sink. Nature. 2021;596(7872):384-388. https://doi.org/10.1038/s41586-021-03737-3
13. Pritchard JN. The Climate is Changing for Metered-Dose Inhalers and Action is Needed. Drug Des Devel Ther. 2020;14:3043-3055. https://doi.org/10.2147/DDDT.S262141
14. Janson C, Henderson R, Löfdahl M, Hedberg M, Sharma R, Wilkinson AJK. Carbon footprint impact of the choice of inhalers for asthma and COPD. Thorax. 2020;75(1):82-84. https://doi.org/10.1136/thoraxjnl-2019-213744
15. Brander M, Davis G. Greenhouse gases, CO2, CO2e, and Carbon: What Do All These Terms Mean? [monograph on the Internet]. Edinburgh: Ecometrica; 2012 [cited 2022 Apr 1]. Available from: https://ecometrica.com/assets/GHGs-CO2-CO2e-and-Carbon-What-Do-These-Mean-v2.1.pdf
16. Jeswani HK, Azapagic A. Life cycle environmental impacts of inhalers. J Clean Prod. 2019;237:117733. https://doi.org/10.1016/j.jclepro.2019.117733
17. The Netherlands. Ministry of Health, Welfare and Sport. National Institute for Public Health and the Environment [homepage on the Internet]. Bilthoven: the Institute [updated 2021 May 27 cited 2022 Apr 1]. The win-win effect of sustainable healthcare: measures and their health effects. Available from: https://www.rivm.nl/documenten/win-win-effect-of-sustainable-health-care-measures-and-their-health-effects
18. UN Environment Programme [homepage on the Internet]. Nairobi: UN Environment Programme; c2019 [cited 2022 May 1]. Medical and Chemicals Technical Options Committee–2018 Assessment Report. Montreal Protocol on Substances that Deplete the Ozone Layer. [Adobe Acrobat document, 182p.]. Available from: https://ozone.unep.org/sites/default/files/2019-04/MCTOC-Assessment-Report-2018.pdf
19. Olivier J, Peters JAHW. Trends in global CO2 and total greenhouse gas emissions: 2020 report [monograph on the Internet]. Bilthoven: PBL Netherlands Environmental Assessment Agency 2020 [cited 2022 May 1]. Available from: https://scholar.google.com.br/scholar?q=Trends+in+global+CO2+and+total+greenhouse+gas+emissions:+2019+report.&hl=en&as_sdt=0&as_vis=1&oi=scholart
20. Ten Have P, van Hal P, Wichers I, Kooistra J, Hagedoorn P, Brakema EA, et al. Turning green: the impact of changing to more eco-friendly respiratory healthcare - a carbon and cost analysis of Dutch prescription data. BMJ Open. 2022;12(6):e055546. https://doi.org/10.1136/bmjopen-2021-055546
21. Centre for Sustainable Healthcare [homepage on the Internet]. Oxford: Centre for Sustainable Healthcare [cited 2022 May 1]. Position statement the environment and lung health 2020. Available from: https://networks.sustainablehealthcare.org.uk/sites/default/files/media/BTS%20Environment%20and%20Lung%20Health%20Position%20Statement%202020.pdf
22. Woodcock A, Janson C, Rees J, Frith L, Löfdahl M, Moore A, et al. Effects of switching from a metered dose inhaler to a dry powder inhaler on climate emissions and asthma control: post-hoc analysis [published online ahead of print, 2022 Feb 7]. Thorax. 2022;thoraxjnl-2021-218088. https://doi.org/10.1136/thoraxjnl-2021-218088
23. Kponee-Shovein K, Marvel J, Ishikawa R, Choubey A, Kaur H, Thokala P, et al. Carbon footprint and associated costs of asthma exacerbation care among UK adults. J Med Econ. 2022;25(1):524-531. https://doi.org/10.1080/13696998.2022.2063603
24. Starup-Hansen J, Dunne H, Sadler J, Jones A, Okorie M. Climate change in healthcare: Exploring the potential role of inhaler prescribing. Pharmacol Res Perspect. 2020;8(6):e00675. https://doi.org/10.1002/prp2.675
25. Wilkinson A, Woodcock A. The environmental impact of inhalers for asthma: A green challenge and a golden opportunity. Br J Clin Pharmacol. 2022;88(7):3016-3022. https://doi.org/10.1111/bcp.15135
26. Plusa T, Badowska-Kozakiewicz A. Can we minimize carbon footprint by using "greener" inhalers and improve clinical outcome at the same time in asthma therapy?. Pol Merkur Lekarski. 2021;49(292):252-254.
27. Rabin AS, Harlan EA, Ambinder AJ. Small Devices, Big Problems: Addressing the Global Warming Potential of Metered-Dose Inhalers. Ann Am Thorac Soc. 2022;19(7):1090-1092. https://doi.org/10.1513/AnnalsATS.202202-131VP
28. National Institute for Health and Care Excellence [homepage on the Internet]. London, UK: National Institute for Health and Care Excellence; c2020 [cited 2022 Apr 1]. Patient decision aid: Inhalers for asthma. Available from: https://www.nice.org.uk
29. Pepper JR, Barrett MA, Su JG, Merchant R, Henderson K, Van Sickle D, et al. Geospatial-temporal analysis of the impact of ozone on asthma rescue inhaler use. Environ Int. 2020;136:105331. https://doi.org/10.1016/j.envint.2019.105331
30. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2021 [cited 2022 Mar 1]. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Available from: https://www.who.int/publications/i/item/9789240034228
31. Walpole SC, Smith K, McElvaney J, Taylor J, Doe S, Tedd H. An investigation into hospital prescribers' knowledge and confidence to provide high-quality, sustainable respiratory care. Future Healthc J. 2021;8(2):e272-e276. https://doi.org/10.7861/fhj.2020-0251
32. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β2-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
33. 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 β2-agonist use in asthma. Eur Respir J. 2020;55(2):1901858. https://doi.org/10.1183/13993003.01858-2019

34. IQVIA Brasil [homepage on the Internet]. São Paulo: IQVIA Brasil; [cited 2021 Dec 1]. Medicamentos empregados no tratamento da asma e comercializados no Brasil. Available from: www.iqvia.com/pt-br/locations/brazil
35. Pereira AB, Basili JOV, Pereira GF, Kalil J, Giavina-Bianchi P, Agondi RC. Comportamento clínico dos pacientes com asma durante a pandemia de COVID-19. Arq Asma Alerg Imunol. 2021;5(1):93-99. https://doi.org/10.5935/2526-5393.20210015
36. North & East Devon Formulary and Referral [homepage on the Internet]. Exeter, UK: [cited 2022 Mar 1]. The environmental impact of inhalers. Available from: https://northeast.devonformularyguidance.nhs.uk/formulary/chapters/3-respiratory/the-environmental-impact-of-inhalers
37. PrescQIPP [homepage on the Internet]. Leeds, UK: PrescQIPP [cited 2022 Mar 1]. Bulletin 295: Inhaler carbon footprint Available from: https://www.prescqipp.info/our-resources/bulletins/bulletin-295-inhaler-carbon-footprint/
38. United States Environmental Protection Agency [homepage on the Internet]. Washington, DC: the Agency [updated 2021 Sep; cited 2022 Mar 1]. Market Characterization of the U.S. Metered-Dose Inhaler Industry. U.S. EPA; 2021. Available from: https://www.epa.gov/sites/default/files/2021-03/documents/epa-hq-oar-2021-0044-0002_attachment_1-mdis.pdf
39. IPCC Sixth Assessment Report [homepage on the Internet]. Geneva: IPCC [cited 2022 Mar 1]. IPCC Report: Climate Chance 2022: Impact, Adaptation and Vulnerability. Available from: https://www.ipcc.ch/report/ar6/wg2/
40. Carroll WD, Gilchrist FJ, Horne R. Saving our planet one puff at a time. Lancet Respir Med. 2022;10(5):e44-e45. https://doi.org/10.1016/S2213-2600(22)00089-3
41. National Health Service (NHS) England [homepage on the Internet]. London: NHS [cited 2022 Mar 1]. Delivering a "Net Zero" National Health Service. Available from: https://www.england.nhs.uk/greenernhs/wp-content/uploads/sites/51/2020/10/delivering-a-net-zero-national-health-service.pdf
42. AstraZeneca [homepage on the Internet]. Cambridge, UK: AstraZeneca [updated 2020 Jan 22, cited 2022 Mar 1]. Ambition Zero Carbon. Available from: https://www.astrazeneca.com/media-centre/articles/2020/ambition-zero-carbon-22012020.html
43. Novartis [homepage on the Internet]. Basel: Novartis [cited 2022 Mar 1]. Climate. Available from: https://www.novartis.com/our-company/corporate-responsibility/environmental-sustainability/climate
44. GlaxoSmithKline (GSK) [homepage on the Internet]. Brentford, UK: GSK [cited 2022 Mar 1]. Environment - our new approach. Available from: https://www.gsk.com/en-gb/responsibility/environment-our-new-approach/
45. AstraZeneca [homepage on the Internet]. Cambridge, UK: AstraZeneca [cited 2022 Mar 1]. Sustainability Report 2019. Available from: https://www.astrazeneca.com/content/dam/az-se/dokument/hallbarhet/AZ_Sustainability%20Report%202019_10.0.pdf
46. GlaxoSmithKline (GSK) [homepage on the Internet]. Brentford, UK: GSK [cited 2022 Mar 1]. Understanding our value chain carbon footprint. Available from: https://www.gsk.com/media/5906/gsk-value-chain-carbon-footprint-2021.pdf
47. Hänsel M, Bambach T, Wachtel H. Reduced Environmental Impact of the Reusable Respimat® Soft Mist™ Inhaler Compared with Pressurised Metered-Dose Inhalers. Adv Ther. 2019;36(9):2487-2492. https://doi.org/10.1007/s12325-019-01028-y

J Bras Pneumol. 2022;48(6):e20220142
https://dx.doi.org/10.36416/1806-3756/e20220142

Telemonitoring in Home Mechanical Ventilation

Katia Vanessa Cantarini[1], Rosineide Pereira Sanches[1], Vanessa Vieira Donini[1], Ruy Pires[2], Heloisa Amaral Gaspar[1]

TO THE EDITOR,

A recent Brazilian survey has shown that, within a year, approximately 300,000 patients undergo home care treatment, and 6% of these patients require ventilatory support (bi-level or life-support ventilators). Importantly, home care treatment has increased by 15-20% on a yearly basis.[1,2]

Despite the increasing demand for home mechanical ventilation (HMV), there are still several barriers to discharging these patients, including operational logistics, keeping the patient safe and clinically stable in a home environment, staff work overload, clinical knowledge for optimizing the ventilation pattern according to the patient's needs, etc.[3] All these factors, in addition to the lack of an evidence-based standard of care, make treating patients on HMV a challenging task.[4]

Telemonitoring patients on HMV may reduce emergency room visits and inpatient admissions and is associated with improved patient management and outcomes, as well as cost savings. The additional possibility of predicting respiratory exacerbation makes telemonitoring a potential tool to revolutionize home-assisted ventilation care.[5]

Home Doctor is one of the largest home care companies in Brazil and provides health care for more than 5,500 patients per year, 10% of whom require ventilatory support. In 2021, the company started an HMV patient-telemonitoring program and, considering the paucity of Brazilian data regarding this topic, we aimed to report the preliminary outcomes of our first 34 patients. From April 2021 to March 2022, we conveniently selected 34 patients on HMV to be enrolled in our telemonitoring program. All patients provided written consent upon enrollment. Physiotherapy management was administered according to current home care protocols and consisted of 40-45 min sessions. Patients received physiotherapy sessions according to their clinical condition, and extra daily visits were provided if clinical worsening was detected. The mean age of the patients was 33.4 years (0-91 years), the predominant sex was female (62%), and the most prevalent diagnosis was neurological/neuromuscular disease (59%). Of all patients, 82% received invasive mechanical ventilation. Nocturnal ventilation was used in 41% of the patients, and continuous ventilation (24 h/day) in 59% (Table 1).

All ventilators (Stellar® and Astral®, ResMed, Sydney, Australia) were coupled to a modem to transmit ventilatory data to the cloud (Airview®) on a daily or on-demand basis. The ventilator parameters and settings (median and interquartile range values per day or minute-by-minute values) could be assessed on a detailed sheet. All alarm activations could also be monitored. Briefly, a clinical physical therapist analyzed the data for each patient 3 times per week and provided the clinical staff with insights during a routine weekly meeting. Any action to be taken was addressed to the attending physical therapist responsible for the patient. Resolution (or not) of the action was discussed in the following meeting. Basically, the topics evaluated in each patient were: HMV settings, compliance (daily hours of use), leakage, tidal volume, respiratory rate, and percentage of spontaneous triggering. The most frequently activated ventilator alarms for each patient were also assessed.

The interventions resulting from monitoring were categorized into: 1) adjustments related to ventilatory support when problems with cuff insufflation, mask fixation, aspiration frequency, or inhalation support were identified; 2) optimization of ventilation parameters, such as inspiratory or expiratory pressure, respiratory frequency, triggering, and tidal volume; 3) alarm adjustments; 4) identification of early clinical deterioration; 5) equipment adjustments (upgrade or downgrade); 6) visualization of equipment manipulation by family members without authorization, and 7) oxygen therapy adjustments (Table 1).

Additionally, a 3-month pre- and post-telemonitoring (pre-TM vs. post-TM) evaluation period of the same 34 patients revealed reductions in extra clinical visits for managing mechanical ventilation (pre-TM = 5; post-TM = 2) and in device problems or malfunctions that required equipment change (pre-TM = 3; post-TM = 2). Although these results are encouraging, one should note that even before telemonitoring, events were rare. Moreover, the descriptive nature of the present study and the absence of a pre/post statistical analysis must be considered.

The efficacy of HMV is dependent on optimal ventilatory support (suitable settings and leak management) to minimize side effects. Thus, ventilator data download functions can be used to assist in clinicians' decision-making to enable the optimal delivery of HMV.[6] Our preliminary results are in line with that. In fact, almost 50% of the analyzed patients were provided optimizations of the HMV settings, be they optimizations of ventilator parameters, leak control, tidal volume, trigger adjustment, or alarm settings. More importantly, we found that caregivers/family members were changing the ventilation parameters without clinician consent in two cases, a fact that could have risked the patients' lives. In another case, an important leak due to cuff inflation system damage was identified, which led to tracheostomy tube replacement.

1. Home Doctor, Brasil.
2. ResMed, São Paulo (SP), Brasil.

ISSN 1806-3756

Table 1. Diagnosis, MV profile, and outcomes of telemonitoring.

Diagnosis	Total patients (%)	IMV (%)	NIV (%)
Neurological Disease	21 (62)	18 (86)	3 (14)
Hypoxic-ischemic encephalopathy	5 (24)	4 (80)	1 (20)
Amyotrophic Lateral Sclerosis	5 (24)	4 (80)	1 (20)
Stroke	4 (19)	4 (100)	0
Spinal Muscular Atrophy type 1	2 (9.5)	2(100)	0
Muscular Dystrophy	1 (4.7)	1(100)	0
Brown-Vialetto-Van Laere Syndrome	1 (4.7)	1(100)	0
Lennox-Gastaut Syndrome	1 (4.7)	1(100)	0
Mitochondrial encephalomyopathy	1 (4.7)	1(100)	0
Guillain-Barre Syndrome	1 (4.7)	0	1(100)
Genetic Disease	8 (23)	5 (62.5)	3 (37.5)
Arnold-Chiari Syndrome	2 (25)	0	2 (100)
Genetic Disorder (under investigation)	1 (12.5)	1 (100)	0
Down Syndrome	1 (12.5)	1 (100)	0
Edwards Syndrome	1 (12.5)	1(100)	0
Patau Syndrome	1 (12.5)	1(100)	0
Krabbe Syndrome	1 (12.5)	1(100)	0
Williams Syndrome	1 (12.5)	0	1 (100)
Osteomuscular disorders	2 (6)	2 (100)	0
Achondroplasia	2	2 (100)	0
Respiratory disease	2 (6)	1 (50)	1 (50)
COPD	1 (50)	0	1 (100)
Bronchopulmonary dysplasia	1 (50)	1 (100)	0
Heart disease	1 (3)	1(100)	0
Congenital heart disease	1 (100)	1 (100)	0
MV Profile & Outcomes			
HMV duration			
Years (mean ± SD)	5.6 ± 5.3	5.7± 5.7	5.4± 3.6
Ventilatory Support			
Daily hours of use (mean ± SD)	19 ± 7	21 ± 6	10 ± 6
Adjustments related to ventilatory support	19 (56)	12 (63)	7 (37)
Daily hours of use	6 (32)	4 (67)	2 (33)
Headgear	5 (26)	0	5 (100)
Inhalation therapy	4 (21)	4 (100)	0
Cuff	2 (10.5)	2 (100)	0
Clearance of secretions	2 (10.5)	2 (100)	0
Ventilation optimization	16 (47)	11 (69)	5 (31)
Mode	1 (6)	1 (100)	0
Parameters	15 (94)	10 (67)	5 (33)
Alarm adjustments	7 (21)	5 (71)	2 (29)
Identification of early clinical deterioration	5 (15)	4 (80)	1 (20)
Equipment adjustments	4 (12)	3 (75)	1 (25)
Upgrade	2 (50)	1 (50)	1 (50)
Downgrade	2 (50)	2 (100)	0
Equipment manipulation by family members	2 (6)	1 (50)	1(50)
Oxygen therapy adjustments	1 (3)	1(100)	0

COPD: Chronic Obstructive Pulmonary Disease; IMV: Invasive Mechanical Ventilation; NIV: Non-invasive Ventilation.

Remote ventilator data analysis also improved operational logistics. Some clinical visits were unnecessary or were more assertive because of the knowledge and data obtained from telemonitoring. Usually, extra visits were related to alarm fatigue in the absence of an attending clinician. In one patient on noninvasive ventilation, alarm excess due to an important leak was observed during nighttime periods but not reported during the clinician's regular daytime visits and was responsible for affecting the sleep quality of the patient and his family. This leak was also responsible for a worsening of the ventilation pattern. The problem was solved after changing the

patient's headgear, which led to an improvement in patient and family sleep quality. Additionally, after the leak was resolved and ventilatory support was adjusted, oxygen support could be suspended. Telemonitoring promoted a feeling of enhanced well-being and safety.

In conclusion, our 1-year preliminary analysis showed that the telemonitoring of patients on HMV was associated with earlier ventilation optimization and improved clinical management, as well as more assertive operational and logistical management.

AUTHOR CONTRIBUTIONS

All authors contributed equally in the investigation, analyses, and writing and approval of the published manuscript.

REFERENCES

1. Censo NEAD-FIPE de Atenção Domiciliar [homepage on the Internet]. São Paulo; 2020 [cited 2022 Mar 15]. Available from: https://www.neadsaude.org.br/wp-content/themes/nead/nead-digital/Censo-NEAD-FIPE-2019-2020/index.html.
2. Carnaúba CMD, Silva TDA, Viana JF, Alves JBN, Andrade NL, Trindade EM. Clinical and epidemiological characterization of patients receiving home care in the city of Maceió, in the state of Alagoas, Brazil. Rev Bras Geriatr Gerontol. 2017;20(3):352-362. https://doi.org/10.1590/1981-22562017020.160163.
3. Yang L, Nonoyama M, Pizzuti R, Bwititi P, John G. Home mechanical ventilation: A retrospective review of safety incidents using the World Health Organization International Patient Safety Event classification. Can J Respir Ther. 2016;52(3):85-91. PMID: 30123023. PMCID: PMC6073515.
4. Lewarski JS, Gay PC. Current issues in home mechanical ventilation. Chest. 2007;132(2):671-6. https://doi.org/10.1378/chest.07-0558.
5. Ackrivo J, Elman L, Hansen-Flaschen J. Telemonitoring for Home-assisted Ventilation: A Narrative Review. Ann Am Thorac Soc. 2021;18(11):1761-1772. https://doi.org/10.1513/AnnalsATS.202101-033CME.
6. Mansell SK, Cutts S, Hackney I, et al. Using domiciliary non-invasive ventilator data downloads to inform clinical decision-making to optimise ventilation delivery and patient compliance. BMJ Open Respir Res. 2018;5(1):e000238. https://doi.org/10.1136/bmjresp-2017-000238.
7. Pinto A, Almeida JP, Pinto S, Pereira J, Oliveira AG, Carvalho M. Home telemonitoring of non-invasive ventilation decreases healthcare utilization in a prospective controlled trial of patients with amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2010;81(11):1238-1242. https://doi.org/10.1136/jnnp.2010.206680.

J Bras Pneumol. 2022;48(6):e20220350
https://dx.doi.org/10.36416/1806-3756/e20220350

Pleural fluid lactate: a diagnostic tool in pleural effusion management?

Sónia Silva Guerra[1], Rita Ferro[1], Tito Abrantes[1], Carla António[1]

TO THE EDITOR:

Malignant pleural effusion (MPE) is a common condition, defined as the accumulation of exudate in pleural space in the presence of cytological or histological evidence of tumor cells, representing an advanced stage. The incidence of MPE is rising, alongside the increase of global cancer incidence and the improvement in overall survival.[1,2]

Infectious pleural effusion (IPE) is also a common clinical problem, as up to 57% of patients with pneumonia develop pleural effusion (PE). It represents a progressive process translating from simple parapneumonic pleural effusion (PPE) into fibrinopurulent collection (complicated PPE), culminating in purulent PE (empyema).[3] The incidence of tuberculosis in Portugal remains high, as tuberculous pleural effusion (TBPE) and lymphadenitis are the most common extrapulmonary manifestations, leading to exudative PE.[4,5]

In the presence of new PE, diagnostic thoracentesis should be performed initially. Currently, available bedside tests using a blood gas analyzer include pH, glucose, and hematocrit. Lactate level is also automatically obtained through this method in most settings. Lactate is a product from the metabolic pathway of anaerobic glycolysis, via lactate dehydrogenase.[6] Bacterial metabolism enhances in IPE, leading to elevation of pleural lactate. In MPE cases, we typically observe chronic progression, potentiating lower levels of lactate.[4] Due to these differences in PE lactate, we hypothesized that MPE lactate would be lower than that in IPE cases, the two most common etiologies observed in our setting.

We aimed to (1) describe the levels of lactate in different etiologies of PE, (2) compare the levels of lactate in IPE and MPE, and (3) determine a cut-off level of lactate in PE to distinguish IPE from MPE.

This study prospectively included all of the patients who underwent diagnostic thoracentesis in our Pulmonology Department in a hospital centre in the city of Viseu, Portugal, between November of 2019 and November of 2020. Patients with PE of known etiology, already under treatment or undergoing evacuating thoracentesis were excluded. Our standard routine protocol for PE analysis includes assessment of glucose, pH, lactate dehydrogenase, protein, cytology and microbiology cultures. Glucose, pH, and hematocrit were measured using a blood gas analyzer (GEM Premier 3500; Werfen, Bedford, MA, USA), which also automatically provides lactate levels (range, 0-15 mmol/L). The study protocol was approved by the research ethics committee of our institution (Protocol no. 03/21/10/2019).

The Light criteria were used to differentiate between transudative and exudative PE.[7] IPE includes all cases of PPE, empyema and TBPE. Patients with PE and pneumonia were classified as having PPE (including complicated PPE), or as having empyema (when purulent pleural fluid or positive cultures were present). TBPE was defined as a positive culture for *Mycobacterium tuberculosis* or positive *M. tuberculosis* DNA (GeneXpert) in PE and pleural biopsy with caseous granuloma, or confirmed pulmonary tuberculosis, with no other alternative cause. MPE was defined as a positive cytological or histological result for malignant cells in PE or an exudative PE in a patient with known advanced tumor with no obvious alternative cause (para-malignant PE). Statistical analysis was performed with the IBM SPSS Statistics software package, version 28.0.0.0 (IBM Corporation, Armonk, NY, USA). All data were expressed as means ± SDs or medians [IQRs].

Of the 129 patients evaluated due to PE, 17 were excluded according to the exclusion criteria. Therefore, 112 patients were included. Most were male (65.2%), with a median age of 73 years [64-81 years]. Exudative PE accounted for 82.1% of cases (n = 92): MPE, in 41 cases; PPE, in 15; empyema, in 7; TBPE, in 7; and other causes, in 22 (cardiac failure, chronic liver disease, chronic kidney disease and pulmonary thromboembolism). Characteristics of the patients, characteristics of pleural fluid according to the distinct types of PE and lactate levels are shown in Table 1.

Pleural fluid lactate levels were significantly higher in the exudate group than in the transudate group ($p < 0.001$) . Regarding the exudate group, patients with MPE had significantly lower levels of lactate than did those with IPE: PPE ($p = 0.030$), TBPE ($p = 0.032$) and empyema ($p < 0.001$). Of the 41 patients with MPE, 56.1% had positive cytological results. No statistical differences in lactate levels were found between para-malignant and malignant PE ($p = 0.121$). Conversely, the patients with exudative PE due to other causes showed significantly lower median levels of lactate than did those with MPE ($p = 0.007$).

A ROC curve analysis was used in order to determine the optimal cut-off point of pleural fluid lactate to differentiate between IPE and MPE. A lactate level ≥ 6.4 mmol/L showed a specificity of 83% and a sensitivity of 55% to predict IPE. The AUC was 0.753 (95% CI: 0.636-0.870; $p < 0.001$).

This study demonstrated the lactate levels in diverse types of PE in a cohort of patients with PE of unknown etiology. To obtain lactate levels, we used a bedside test that has been in use in our department to measure

1. Serviço de Pneumologia, Centro Hospitalar Tondela-Viseu, Viseu, Portugal.

Table 1. Patient characteristics and biochemistry results of pleural fluid samples classified in accordance with the Light[7] criteria and subgroups.[a]

Characteristic	Total	Group		Subgroup				
		Transudate	Exudate	MPE	PPE	Empyema	TBPE	Other causes[b]
Patient	(n = 112)	(n = 20)	(n = 92)	(n = 41)	(n = 15)	(n = 7)	(n = 7)	(n = 22)
Gender								
Male	73 (62.5)	13 (65.0)	60 (65.2)	23 (56.1)	11 (73.3)	4 (57.1)	6 (85.7)	16 (72.7)
Female	39 (34.5)	7 (35.0)	32 (34.8)	18 (43.9)	4 (26.7)	3 (42.9)	1 (14.3)	6 (27.3)
Age, years	73 [64-81]	75.6 ± 11.1	73 [64-80]	72.2 ± 12.6	67.3 ± 14.0	66 ± 22.7	58.1 ± 18.8	78.5 [70-83]
Pleural fluid biochemistry								
pH	7.40 [7.27-7.47]	7.44 ± 0.14	7.39 [7.25-7.46]	7.41 [7.29-7.46]	7.22 ± 0.24	6.86 ± 0.46	7.25 ± 0.13	7.43 ± 0.06
Glucose, mg/dL	99.3 ± 52.3	127.1 ± 29.8	93.3 ± 54.2	101 [76-119]	85.1 ± 64.0	5 [5-37]	46.3 ± 25.4	108 [93-150]
LDH, U/L	293 [158-642]	122.6 ± 57.8	336 [196-727]	337 [216-443]	758 [285-1058]	2819 [2118-32110]	792 ± 358	230.7 ± 153.6
Protein, g/dL	3.8 ± 1.2	2.6 ± 1.1	4.0 ± 1.1	3.9 ± 1.0	4.2 ± 0.9	3.7 ± 1.4	4.8 ± 0.6	3.9 ± 1.2
Lactate, mmol/L	3.0 [1.6-5.8]	1.6 [1.1-2.0]	3.5 [2.0-6.5]	3.4 [2.0-5.8]	6.3 ± 4.5	12.5 ± 2.8	6.6 ± 2.7	2.2 ± 1.1
p[c]					0.030	< 0.001	0.032	0.007

MPE: malignant pleural effusion; PPE: parapneumonic pleural effusion; and TBPE: tuberculous pleural effusion. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Cardiac failure, chronic liver disease, chronic kidney disease and pulmonary thromboembolism. [c]p values calculated by comparing the lactate levels in the MPE subgroup with those in the other subgroups.

glucose, pH and hematocrit. In our study, the most common forms of PE had infectious or malignant origins. We demonstrated significantly higher median levels of lactate in IPE than in MPE, which might be explained by high metabolic cell activity during pleural infection, accompanied by bacterial metabolism producing lactic acid. Otherwise, MPE represents chronic inflammation with lower cell production of lactate. As demonstrated in other studies, cases of transudative PE showed the lowest levels of lactate, supported by the underlying pathophysiology, with no pleural disease or minimal inflammation.[4]

We demonstrated that a lactate cut-off level ≥ 6.4 mmol/L can help clinicians differentiate between IPE and MPE, eventually guiding the decision of whether antibiotic treatment should be initiated even if there is no obvious indication, or whether chest pleural drainage should be carried out in cases of complicated PPE and empyema. If lactate levels are < 6.4 mmol/L, other etiologies (such as malignancy) should be suspected, and other tests (such as cytology, pleural biopsy and thoracoscopy) should be performed.

This study has several limitations. Firstly, despite being a prospective study, it had a limited sample size. Secondly, other less common exudative causes were not investigated, which could have introduced biases.

In conclusion, rapid bedside evaluation of lactate levels in patients with PE can be a diagnostic tool in differentiating infection from other causes, particularly malignancy. Therefore, this fact may impact the subsequent management in the event of a new PE, especially following an initial thoracentesis.

AUTHOR CONTRIBUTIONS

SSG: study conception, data collection, statistical analysis, and drafting of the manuscript. RF: data collection, statistical analysis, and drafting of the manuscript. TA and CA: revision of the manuscript. All of the authors read and approved the final version.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Psallidas I, Kalomenidis I, Porcel JM, Robinson BW, Stathopoulos GT. Malignant pleural effusion: from bench to bedside [published correction appears in Eur Respir Rev. 2016 Sep;25(141):360] [published correction appears in Eur Respir Rev. 2016 Sep;25(141):360]. Eur Respir Rev. 2016;25(140):189-198. https://doi.org/10.1183/16000617.0019-2016
2. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J. 2018;52(1):1800349. https://doi.org/10.1183/13993003.00349-2018
3. Davies HE, Davies RJ, Davies CW; BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii41-ii53. https://doi.org/10.1136/thx.2010.137000

4. Kho SS, Chan SK, Yong MC, Cheah HM, Lee YG, Tie ST. Pleural fluid lactate as a point-of-care adjunct diagnostic aid to distinguish tuberculous and complicated parapneumonic pleural effusions during initial thoracentesis: Potential use in a tuberculosis endemic setting. Respir Investig. 2020;58(5):367-375. https://doi.org/10.1016/j.resinv.2020.01.004
5. European Centre for Disease Prevention and Control. WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2021 - 2019 data. Copenhagen: WHO Regional Office for Europe; 2021.
6. Gupta GS. The Lactate and the Lactate Dehydrogenase in Inflammatory Diseases and Major Risk Factors in COVID-19 Patients. Inflammation. 2022;1-33. https://doi.org/10.1007/s10753-022-01680-7
7. Light RW. The Light criteria: the beginning and why they are useful 40 years later. Clin Chest Med. 2013;34(1):21-26. https://doi.org/10.1016/j.ccm.2012.11.006

J Bras Pneumol. 2022;48(6):e20220248
https://dx.doi.org/10.36416/1806-3756/e20220248

Impact of the COVID-19 pandemic on the diagnosis of lung cancer in northeastern Brazil

Iusta Caminha[1,2], Fabio Távora[1,3], Juliana Sousa[4], Francisco Martins Neto[3], Luciano Pamplona de Goes Cavalcanti[1,5]

TO THE EDITOR:

Lung cancer is the most lethal and one of the most common cancers in both men and women. More than 35,000 deaths and 30,000 new cases occurred in Brazil in 2020. Ceará, a state in northeastern Brazil, has the sixth highest incidence of lung cancer in the country.[1]

At the end of 2019, SARS-CoV-2 infection began to advance rapidly. By March of 2022, SARS-CoV-2 had infected approximately 30 million people in Brazil, with more than 3 million cases and almost 27,000 deaths in the state of Ceará. The city of Fortaleza, one of the seven largest capitals in Brazil, had the second highest mortality rate in the first year of the COVID-19 pandemic in the country, second only to that in the city of Manaus.[2]

The COVID-19 pandemic demanded urgent adaptation of health care services. There was a decrease in clinical appointments, diagnostic procedures, and hospitalizations for other diseases. The flow of care was changed at health care facilities, and hospital beds were reserved for COVID-19 patients: a challenging scenario for the diagnosis of cancer.

The reduction in screening tests and diagnostic procedures impacted incidence rates, with a significant drop in the diagnosis of new cancer cases worldwide.[3] In Brazil, at least 15,000 cancer cases went undiagnosed per month in 2020. The northeastern region of the country was the most affected, with a 42.7% reduction in the mean number of monthly diagnoses.[4]

With regard to lung cancer in particular, the numbers of bronchoscopies and lung biopsies performed in the Brazilian Unified Health Care System between March and May of 2020 decreased significantly, by 35% and 13%, respectively, when compared with those for the same period in the previous year. Hospital admissions for lung cancer also dropped significantly (by 7%) over the same period.[5] Although the recommendation was that treatments that confer a survival benefit should continue to be provided whenever possible,[6] the readjustment and overload of the Brazilian Unified Health Care System during the COVID-19 pandemic seem to have delayed the diagnosis and treatment of lung cancer.

In addition to having an impact on the incidence of cancer, the COVID-19 pandemic in England resulted in a significant increase in the number of preventable deaths resulting from late diagnosis of various types of cancer.[7] Patients with lung cancer were shown to be at a greater risk for pandemic-related care delays than were those with other malignancies.[8] Furthermore, after the beginning of the COVID-19 pandemic, patients presented with more advanced disease at the time of diagnosis.[9]

In the present study, we evaluated the impact of the COVID-19 pandemic on the diagnosis of lung cancer. Data were collected retrospectively from the files of the surgical pathology department of the *Hospital de Messejana*, located in the city of Fortaleza, Brazil. Our study was approved by the local research ethics committee (Protocol no. CAAE 52992721.0.0000.5039). The surgical pathology reports were identified by sequential numbers by sign-out date. Patient anonymity and confidentiality were strictly maintained. Data were also collected from publicly available anonymized hospital records.[10]

The *Hospital de Messejana* is a referral hospital for thoracic diseases in the northern and northeastern regions of Brazil, playing a major role in lung cancer screening and management. Between 2018 and 2021, the hospital accounted for approximately 90% of all bronchoscopies performed in the state of Ceará and more than 80% of all hospitalizations for investigation and surgical treatment of lung cancer in the state.[10]

As of June of 2020, because of the COVID-19 pandemic, the *Hospital de Messejana* medical wards and ICUs were adapted to receive patients with COVID-19. As a result, there was a reduction in the number of diagnostic procedures for other diseases. The surgical pathology department of the hospital received a significantly lower number of samples for analysis in 2020 and 2021. Consequently, the numbers of surgical pathology reports issued in 2020 and 2021 decreased significantly in comparison with those of reports issued before the COVID-19 pandemic (Figure 1A).

Between 2015 and 2019, 3,703 ± 70 surgical pathology reports were issued annually. In 2020 and 2021, the numbers of reports issued were 2,748 and 2,899, respectively. The greatest reduction was observed in 2020. May was the most affected month, followed by June and April, coinciding with the peak months of the first wave of the COVID-19 pandemic in the state of Ceará. In 2021, although there was a slight improvement in the total number of examinations in comparison with 2020,

1. Departamento de Patologia, Universidade Federal do Ceará, Fortaleza (CE) Brasil.
2. Universidade de Fortaleza – UNIFOR – Fortaleza (CE) Brasil.
3. Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza (CE) Brasil.
4. Argos Patologia, Fortaleza (CE) Brasil.
5. Centro Universitário Christus – Unichristus – Fortaleza (CE) Brasil.

ISSN 1806-3756

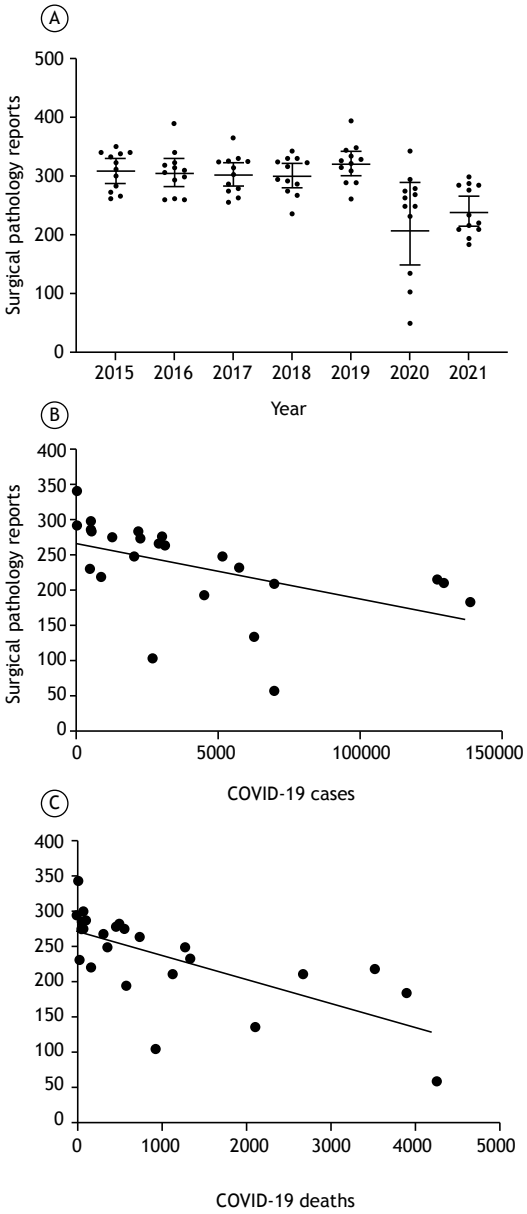

Figure 1. Numbers of surgical pathology reports issued by pathologists at the *Hospital de Messejana* before and during the COVID-19 pandemic, and their relationship with the total numbers of COVID-19 cases and deaths in the state of Ceará, Brazil. In A, surgical pathology reports issued between 2015 and 2021. Each dot represents the number of reports issued each month. There was a significant reduction in the numbers of reports issued in 2020 and 2021 in comparison with those issued in the 2015-2019 period ($p < 0.05$). There was no significant difference between the numbers of reports issued in 2020 and 2021. In B and C, linear relationship of the numbers of surgical pathology reports issued by pathologists at the Hospital de Messejana with the numbers of COVID-19 cases (B) and deaths (C) occurring between January of 2020 and December of 2021. Each dot represents one month in the analyzed period.

there was no significant recovery. As can be seen in Figure 1B, there was a strong negative correlation between the number of surgical pathology reports and the number of COVID-19 cases ($r(22) = -0.502$; $p = 0.012$), as well as between the number of surgical pathology reports and the number of deaths from COVID-19 ($r(22) = -0.689$; $p = 0.002$).

The mean number of bronchoscopies performed monthly at the *Hospital de Messejana* in 2020 and 2021 was 47.61, which was 44% lower than those for 2018 and 2019, before the COVID-19 pandemic ($p = 0.0006$). Statistically significant reductions were also seen in the numbers of surgical pathology reports on the lungs, trachea, pleura, and mediastinal lymph nodes, as well as in the number of hospitalizations for the diagnosis and management of lung cancer (International Classification of Diseases, 10th revision codes C33 and C34), which decreased by 17% ($p = 0.006$) and 21% ($p = 0.005$), respectively.

The positivity rate (i.e., the ratio of the total number of cancer cases to the total number of surgical pathology reports) did not change during the COVID-19 pandemic. In 2020 and 2021, the mean proportion of positive cases or strongly suspected cases of malignancy for biopsies performed in the lungs, pleura, trachea, and mediastinal lymph nodes was 48.6%, which is not significantly different from the positivity rates for 2018 and 2019 (48.2%; $p = 0.75$). However, fewer cases were diagnosed, because of the negative impact of COVID-19 on the total number of biopsies analyzed.

For non-small cell lung carcinoma, which is the predominant histological type, the 5-year survival rate is reduced by almost half in cases of locally advanced tumors in comparison with those diagnosed at an earlier stage, being equal to 37%. The 5-year survival rate is even lower in advanced stages, dropping to an alarming 8%.[11] This underscores the negative impact that a reduction in the diagnosis of lung cancer at the *Hospital de Messejana* during the pandemic years of 2020 and 2021 can have on prognosis and cure rates.

The state of Ceará, as well as several other regions of the world, will face a great challenge. Patients who failed to receive a diagnosis during the pandemic years of 2020 and 2021 are likely to present with more advanced disease at diagnosis, with worse prognosis and lower mean survival rates. There is an urgent need for restructuring the health care system (with the return of early detection programs) and preparing specialized centers to manage the backlog of patients with lung cancer.

In Brazil, lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death among women. Therefore, there is a need for campaigns promoting early diagnosis of lung cancer, similar to the Prostate Cancer Awareness Month and the Breast Cancer Awareness Month campaigns. Increased education on lung cancer, together with an increased availability of outpatient visits, diagnostic tests, and surgical procedures for lung cancer, could mitigate the impact of the COVID-19 pandemic on lung cancer screening and management.

AUTHOR CONTRIBUTIONS

All of the authors contributed equally to the conception of the study, as well as the drafting, revision, and approval of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA) [homepage on the Internet]. Rio de Janeiro: INCA; c2022 [cited 2022 Apr 6]. Estatística do cancer. Available from: https://www.inca.gov.br/numeros-de-cancer
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde [homepage on the Internet]. Brasília: Ministério da Saúde; c2022 [cited 2022 Apr 8]. Painel Coronavírus. Available from: https://covid.saude.gov.br/
3. Kaufman HW, Chen Z, Niles J, Fesko Y. Changes in the Number of US Patients With Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic [published correction appears in JAMA Netw Open. 2020 Sep 1;3(9):e2020927]. JAMA Netw Open. 2020;3(8):e2017267. https://doi.org/10.1001/jamanetworkopen.2020.17267
4. Marques NP, Silveira DMM, Marques NCT, Martelli DRB, Oliveira EA, Martelli-Júnior H. Cancer diagnosis in Brazil in the COVID-19 era. Semin Oncol. 2021;48(2):156-159. https://doi.org/10.1053/j.seminoncol.2020.12.002
5. Araujo-Filho JAB, Normando PG, Melo MDT, Costa AN, Terra RM. Lung cancer in the era of COVID-19: what can we expect?. J Bras Pneumol. 2020;46(6):e20200398. https://doi.org/10.36416/1806-3756/e20200398
6. Aran V, De Marchi P, Zamboni M, Ferreira CG. Dealing with lung cancer in the COVID-19 scenario (A review). Mol Clin Oncol. 2021;14(2):27. https://doi.org/10.3892/mco.2020.2189
7. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study [published correction appears in Lancet Oncol. 2021 Jan;22(1):e5]. Lancet Oncol. 2020;21(8):1023-1034. https://doi.org/10.1016/S1470-2045(20)30388-0
8. Bhalla S, Bakouny Z, Schmidt AL, Labaki C, Steinharter JA, Tremblay DA, et al. Care disruptions among patients with lung cancer: A COVID-19 and cancer outcomes study. Lung Cancer. 2021;160:78-83. https://doi.org/10.1016/j.lungcan.2021.07.002
9. Reyes R, López-Castro R, Auclin E, García T, Chourio MJ, Rodriguez A, et al. Impact of COVID-19 Pandemic in the Diagnosis and Prognosis of Lung Cancer. J Thorac Oncol. 2021;16(3):S141. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1556086421002616 https://doi.org/10.1016/j.jtho.2021.01.219
10. Secretaria da Saúde do estado do Ceará (SESA) [homepage on the Internet]. Fortaleza: SESA; c2022 [cited 2022 Feb 9]. Sistema de Informações Hospitalares Available from: https://www.saude.ce.gov.br/tabnet-ceara/sih/
11. American Cancer Society [homepage on the Internet]. Atlanta: American Cancer Society; c2022 [cited 2022 Apr 6]. Lung Cancer Survival Rates. Available from: https://www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html

J Bras Pneumol. 2022;48(6):e20220232
https://dx.doi.org/10.36416/1806-3756/e20220232

Tuberculous empyema: combined intrapleural therapy might be an alternative

Philippe de Figueiredo Braga Colares[1], Jennifer Kiara Delgado Rivas[1], Amanda dos Santos Sciortino[1], Roberta Karla Barbosa de Sales[1], Lisete Ribeiro Teixeira[1]

TO THE EDITOR,

Tuberculous empyema (TE) is characterized by the presence of pus in the pleural cavity as a consequence of chronic active infection of the pleura by *Mycobacterium tuberculosis*, resulting in an influx of neutrophils and subsequent development of purulent effusion, thickening, and eventually, pleural calcification.[1] Nevertheless, the pathophysiology of TE is not yet completely understood. It is postulated that infection of the pleural cavity by mycobacteria may occur through several mechanisms, including the progression of improperly treated tuberculous pleural effusions; direct dissemination of the infection from a ruptured thoracic lymph node, rupture of the pulmonary cavity, or a subdiaphragmatic focus; hematogenous spread from a distant focus; or even contamination of the pleural cavity after pulmonary surgery/pneumonectomy.[1,2]

The treatment of pleural involvement by tuberculosis is similar to that of pulmonary disease; however, when it comes to TE, there are no extensive recommendations in the literature for pleural management, and evidence of the treatment of bacterial empyema is usually extrapolated.[1] Despite being the initial recommendation, one-third of patients with TE have failed pleural drainage.[2] Invasive procedures, such as open thoracotomy with pleural decortication and, more recently, video-assisted thoracoscopic surgery (VATS), may be necessary to resolve the infectious process and prevent progression to fibrothorax. Still, the risks and costs are not negligible.[3,4] As in bacterial empyema, the use of combined intrapleural therapy with fibrinolytics and deoxyribonuclease (DNase), in synergy with oral medication, could be part of the therapeutic arsenal for patients with initial failure of chest drainage.[5]

A 36-year-old male with no known comorbidities and a history of fever and productive cough for 12 months was subjected to several treatments for community-acquired pneumonia, without success and with recurrence of symptoms, associated with a weight loss of 12 kg in that period. Three sputum samples were tested for acid-fast bacilli (AFB) smears, nucleic acid amplification tests (Xpert MTB/RIF Ultra), and mycobacterial cultures, and all results were negative. Initial chest radiography revealed an opacity in the left apex associated with moderate ipsilateral pleural effusion. Due to the high prevalence of pleural tuberculosis in Brazil, a standard regimen with rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) was started for 2 months, followed by maintenance therapy with RI. Four months after the start of treatment, despite the clinical resolution of the fever, the patient maintained weight loss, dyspnea, and hyporexia, in addition to the persistence of a large left pleural effusion. The patient was then forwarded to a tertiary service for investigation.

Bedside point-of-care ultrasound showed a moderate amount of pleural effusion, with homogeneous echogenicity, internal septations, and swirling echoes, in addition to significant pleural thickening (complex pleural effusion). Computed tomography (CT) of the chest confirmed the presence of moderate left loculated pleural effusion associated with pleural thickening and enhancement, as well as bilateral centrilobular pulmonary micronodules with a "tree-in-bud" aspect that were sometimes confluent in areas of pulmonary consolidation. The presence of left upper lobe fibroatelectasis was also observed. Diagnostic thoracentesis was performed, with drainage of 60 mL of purulent fluid. Pleural fluid analysis showed an exudate (Light's criteria) with pH 7.12, 4,774 U/L of lactic dehydrogenase, 5.8 mg/dL of protein, 321 U/L of adenosine deaminase (ADA), and cytology of 115,200 cells, 98% of which were leukocytes (100% polymorphonuclear). In addition, the Xpert MTB/RIF Ultra assay was positive. Thoracic drainage with a small 14F pigtail catheter was indicated, with an immediate output of 200 mL of purulent fluid, despite a significant reduction in output on the second day and persistence of pleural effusion in a control radiograph. The patient was provided intrapleural therapy with 10 mg of tissue plasminogen activator (Actilyse®) and 5 mg of DNase (Pulmozyme®), injected through the chest tube, associated with pleural lavage with 250 mL of 0.9% saline solution, for 3 days. The patient progressed with a significant increase in pleural output (1,130 mL in 5 days) and rapid clinical and radiological improvement without complications associated with local therapy. The chest tube was removed after the fifth day of treatment, and the patient was discharged after 7 days of hospitalization without the need for additional interventions, with maintenance of oral therapy (RI).

Although its pathophysiology is not well understood, TE is a serious condition that, aside from high mortality, can result in severe pleural sequelae.[1,2] Despite its high efficacy in the treatment of pleural tuberculosis, drug therapy (RIPE) may be insufficient for the management of TE. Recent studies have confirmed the effectiveness of VATS as a therapeutic option in cases of chest drainage failure;[1,2] however, this therapy is reserved for patients with low surgical risk, in addition to being an inaccessible and expensive option for the vast majority of the Brazilian population.[2,4] Although well-established for the management of infected pleural effusion

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

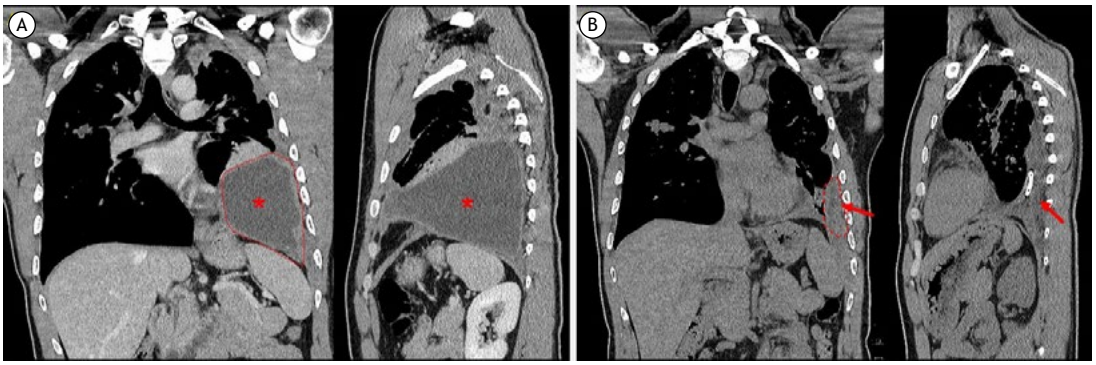

Figure 1. Chest CT (coronal and sagittal) before intrapleural therapy, showing the presence of moderate left loculated pleural effusion (red asterisk and dotted line) (A). Chest CT (coronal and sagittal) after intrapleural therapy, showing the pigtail catheter and a significant reduction in pleural effusion (red arrow and dashed line) (B).

(parapneumonic),[3-7] few studies have evaluated the efficacy of intrapleural therapy for patients diagnosed with TE, either with fibrinolysis alone or in association with DNase, limited to a few case series.[5]

Here, we report the case of a patient diagnosed with TE with persistent symptoms and pleural effusion, despite Directly Observed Therapy (DOT). As a first step, the insertion of a chest tube was indicated but was insufficient for the complete resolution of the condition. In this case, some surgical procedures, such as VATS, could be necessary to resolve this pleural infection. However, the adjuvant intrapleural therapy with alteplase and DNase for 3 days resulted in clinical, laboratory, and radiological improvement associated with a short hospital stay, without the need for a more invasive surgical procedure and without adverse effects.

There is no consensus on the intrapleural dose that should be used.[3,6] Thus, larger studies need to be carried out to assess the efficacy and safety of the intrapleural use of alteplase-DNase in TE as an alternative therapy to surgical interventions.

AUTHOR CONTRIBUTIONS

PFBC: study design, data collection, writing, and manuscript review. JKDR and ASS: data collection and writing the manuscript. RKBS and LRT: study design and manuscript review.

REFERENCES

1. Shaw JA, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusion. Respirology. 2019 Oct;24(10):962-971. https://doi.org/10.1111/resp.13673.
2. Wen P, Wei M, Han C, He Y, Wang MS. Risk factors for tuberculous empyema in pleural tuberculosis patients. Sci Rep. 2019 Dec 20;9(1):19569. https://doi.org/10.1038/s41598-019-56140-4.
3. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011 Aug 11;365(6):518-26. https://doi.org/10.1056/NEJMoa1012740.
4. Luengo-Fernandez R, Penz E, Dobson M, Psallidas I, Nunn AJ, Maskell NA, et al. Cost-effectiveness of intrapleural use of tissue plasminogen activator and DNase in pleural infection: evidence from the MIST2 randomised controlled trial. Eur Respir J. 2019 Aug 1;54(2):1801550. https://doi.org/10.1183/13993003.01550-2018.
5. Cheong XK, Abdul Hamid MF. Intrapleural alteplase and DNase for complex tuberculous pleurisy: a medical approach. Respirol Case Rep. 2021 Jan 3;9(2):e00706. https://doi.org/10.1002/rcr2.706. eCollection 2021 Feb.
6. Faisal M, Farhan R, Cheong XK, Ng BH, Nuratiqah N, Andrea YI B. Short-course modified regimen intrapleural alteplase and pulmozyme (DNase) in pleural infection. Respir Med Case Rep. 2020 Jul 17;31:101168. https://doi.org/10.1016/j.rmcr.2020.101168.
7. Altmann ES, Crossingham I, Wilson S, Davies HR. Intra-pleural fibrinolytic therapy versus placebo, or a different fibrinolytic agent, in the treatment of adult parapneumonic effusions and empyema. Cochrane Database Syst Rev. 2019 Oct 30;2019(10):CD002312. https://doi.org/10.1002/14651858.CD002312.pub4.

J Bras Pneumol. 2022;48(6):e20220294
https://dx.doi.org/10.36416/1806-3756/e20220294

Acute dyspnea during the general anesthesia recovery period: do not overlook negative pressure pulmonary edema

Bruno Lima Moreira[1], Felipe Marques da Costa[2], Deodato Rolim Cartaxo[1], Bruna Brandão Libânio[1], Pablo Rydz Pinheiro Santana[1,3]

TO THE EDITOR:

Negative pressure pulmonary edema (NPPE) is a type of noncardiogenic edema that may occur after an abrupt increase in negative pressure within the pleural space secondary to contraction of the inspiratory muscles in an attempt to overcome an acute obstruction in the upper airway. NPPE is a potentially serious complication during the recovery period from general anesthesia, occurring in up to 0.1% of patients undergoing orotracheal intubation, also accounting for 5-10% of all episodes of upper airway obstruction.[1,2]

During anesthetic practice, NPPE is more common in young and healthy men, who have greater muscle mass and therefore generate greater variations in intrapleural negative pressure.[2] Although NPPE usually develops shortly after extubation, this phenomenon can eventually occur after a few hours. The major symptoms are dyspnea and cough with foaming serosanguineous secretion. Upon physical examination, tachycardia, snoring, rales, and stridor may be present. In most severe forms, bradycardia, paradoxical breathing, and cyanosis can be observed.[1-5]

We herein report the case of a 26-year-old man with no previous comorbidities who underwent elective bilateral flexible ureterorenoscopy and lithotripsy with the insertion of a double J catheter for the treatment of right renal and left ureteral stones. The procedure was performed under balanced general anesthesia with laryngeal mask airway (LMA) use. SpO_2 and blood pressure before anesthetic induction were 99% and 130/80 mmHg, respectively. There was no sign of aspiration of gastric contents during the procedure. Fluid balance remained close to zero, and no significant blood pressure changes were observed. The patient evolved with an acute episode of respiratory distress (tachydyspnea, cough, and frothy, bloody sputum; SpO_2 dropped to 86%) in the recovery room while waking up from general anesthesia 15 min after LMA removal. Pulmonary auscultation showed crackling rales predominantly at the base of the right hemithorax. There was no stridor at that time. Arterial blood gas analysis revealed partial pressure of oxygen of 41 mmHg and arterial oxygen saturation of 74% in room air. Oxygen supplementation was started with a non-rebreathing mask with a flow of 5 L/min.

Bedside chest radiography was performed and showed subtle ill-defined opacities more evident in the lower right lung field (Figure 1A). The patient underwent assisted ventilation with 10 cmH_2O CPAP and 100% oxygen. After 30 min, there was an improvement in SpO_2 (98%), with reduction of respiratory distress. Intubation was not considered due to the clinical improvement. Then, he underwent pulmonary CT angiography, which was negative for pulmonary embolism and showed several small, sometimes coalescing, consolidative opacities associated with ground-glass opacities affecting all of the lobes in both lungs, predominantly in peribronchovascular regions, more extensive in the lower lobes (Figure 1B-1D). Laboratory tests revealed 9,600 cells/μL leukocytes, 13.5 g/dL hemoglobin, and normal platelet count. Serum electrolytes, renal function, echocardiogram, and electrocardiogram were normal. The patient was referred to the ICU, and CPAP was maintained in 60-min sessions every 8 h, with weaning from oxygen therapy after 24 h. He was discharged after two days with complete resolution of symptoms and radiological abnormalities.

In summary, the clinical scenario was an acute episode of respiratory distress in a young male patient during the general anesthesia recovery period with LMA use. The main differential diagnoses, including pulmonary embolism and cardiogenic edema, were ruled out. Due to the clinical course of rapid resolution of pulmonary edema combined with a clear causative factor and exclusion of differential diagnoses, it was concluded that the negative pressure mechanism after a transient laryngospasm was responsible for the clinical presentation. Thus, the presumptive diagnosis was NPPE, a form of noncardiogenic pulmonary edema.

NPPE has been subdivided into two types. Type 1 is related to vigorous inspiratory effort in case of acute airway obstruction, such as post-extubation laryngospasm or epiglottitis, and type 2 occurs after the relief of chronic partial airway obstruction, such as after adenoidectomy.[6-8] The case presented herein was type 1 NPPE.

Type 1 NPPE most commonly occurs in young patients during the recovery period from general anesthesia with orotracheal intubation. However, with the accelerated adoption curve of LMA in clinical practice, several cases of NPPE with LMA use have been reported.[8-10]

The pathogenesis of type 1 NPPE is multifactorial. Inspiratory effort to overcome the obstruction generates

1. BP Medicina Diagnóstica, Hospital Beneficência Portuguesa de São Paulo, São Paulo (SP) Brasil.
2. Serviço de Pneumologia, Hospital Beneficência Portuguesa de São Paulo, São Paulo (SP) Brasil.
3. Grupo Fleury, São Paulo (SP) Brasil.

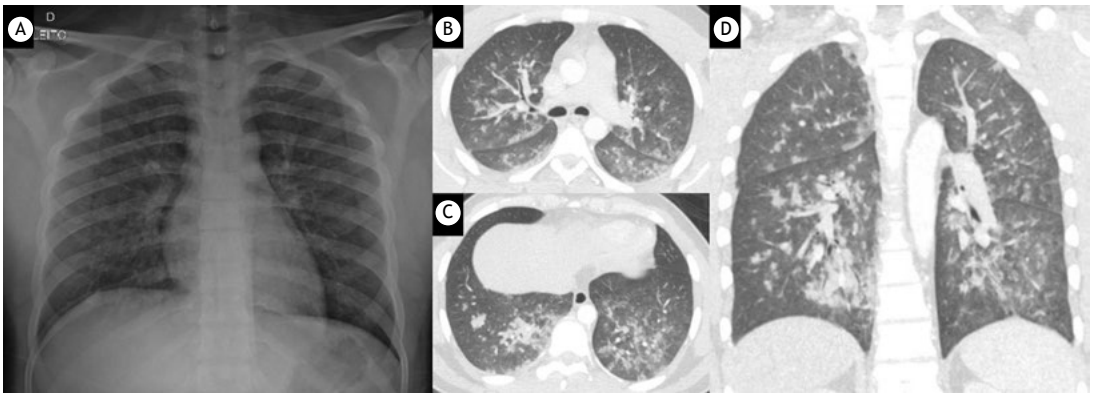

Figure 1. In A, Anteroposterior chest radiograph (bedside) demonstrated subtle ill-defined opacities, more evident in the lower right lung field. In B, C, and D, pulmonary CT angiography images (lung window) in axial (B and C) and coronal (D) planes revealed several small, sometimes coalescing, consolidative opacities associated with ground-glass opacities affecting all of the lobes in both lungs, predominantly in peribronchovascular regions, more extensive in the lower lobes. These findings are consistent with pulmonary edema (in this case, negative pressure pulmonary edema). It is worth mentioning that the exam was negative for pulmonary embolism.

an increase in intrapleural negative pressure. The "siphon effect" within the rib cage increases venous return to the right heart chambers, which produces an increase in hydrostatic pressure in the pulmonary capillaries and causes fluid to move out of the vessels into the interstitial and alveolar space, causing edema, imbalance between ventilation and perfusion, and, consequently, hypoxemia. It may trigger hypoxic pulmonary vasoconstriction and raise pulmonary vascular resistance. By increasing the right ventricular volume, the interventricular septum may shift leftward, with reduced left ventricular diastolic compliance. Increased cardiac afterload and myocardial hypoxia lead to decreased left ventricular function, with increased pulmonary venous pressure. Hypercapnia, acidosis, hyperadrenergic response, and loss of capillary integrity may be contributing factors in the pathophysiology.[1-3,6,8]

NPPE has a quick onset, commonly within minutes, and a relatively rapid resolution. If recognized and treated early, NPPE is usually a self-limited condition and, thus, reversible, with relevant clinical and radiological improvement, frequently in 12-48 h. The diagnosis of NPPE can be made on the basis of the presence of a precipitating situation and compatible symptoms. Chest radiograph and/or CT findings of pulmonary edema support the diagnosis.[1,4,6,8]

The management of NPPE is mainly supportive and includes its early recognition followed by upper airway clearance, supplemental oxygen therapy, and use of noninvasive ventilation (including CPAP). In extreme cases, (re)intubation with a certain level of PEEP may be required. Muscle relaxation with low doses of succinylcholine can relieve laryngospasm.[1-6,8] The role of steroids and diuretics is still controversial, and there is no clear recommendation regarding their use.[1]

In conclusion, medical practitioners should be aware of NPPE, and a correct understanding of pathophysiological mechanisms behind this condition is essential for early diagnosis and proper management.

AUTHOR CONTRIBUTIONS

BBL, BLM, and DRC: conception, study planning and design, data collection, selection of the images, and literature review. BLM, DRC, and FMC: writing of preliminary drafts and final version of the manuscript. BLM, FMC, and PRPS: revision of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Liu R, Wang J, Zhao G, Su Z. Negative pressure pulmonary edema after general anesthesia: A case report and literature review. Medicine (Baltimore). 2019;98(17):e15389. https://doi.org/10.1097/MD.0000000000015389
2. Peixoto AJ. Asymmetric negative pressure pulmonary edema after acute upper airway obstruction: case report [Article in Portuguese]. Rev Bras Anestesiol. 2002;52(3):335-343. https://doi.org/10.1590/s0034-70942002000300009
3. Silva LAR, Guedes AA, Salgado Filho MF, Chaves LFM, Araújo FP. Negative pressure pulmonary edema: report of case series and review of the literature [Article in Portuguese]. Braz J Anesthesiol. 2019;69(2):222-226. https://doi.org/10.1016/j.bjan.2018.11.005
4. Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-Pressure Pulmonary Edema. Chest. 2016;150(4):927-933. https://doi.org/10.1016/j.chest.2016.03.043
5. Bisinotto FMB, Cardoso RP, Abud TM. Acute pulmonary edema associated with obstruction of the airways. Case report. Rev Bras Anestesiol. 2008;58(2):165-171. https://doi.org/10.1590/s0034-70942008000200009
6. Bhaskar B, Fraser JF. Negative pressure pulmonary edema revisited: Pathophysiology and review of management. Saudi J Anaesth. 2011;5(3):308-313. https://doi.org/10.4103/1658-354X.84108
7. Mussi RK, Toro IF. Negative-pressure pulmonary edema and hemorrhage associated with upper airway obstruction. J Bras

Pneumol. 2008;34(6):420-424. https://doi.org/10.1590/s1806-37132008000600013

8. Vandse R, Kothari DS, Tripathi RS, Lopez L, Stawicki SPA, Papadimos TJ. Negative pressure pulmonary edema with laryngeal mask airway use: Recognition, pathophysiology and treatment modalities. Int J Crit Illn Inj Sci. 2012;2(2):98-103. https://doi.org/10.4103/2229-5151.97275
9. Jain R, Kumar M, Haq ZA, Banerjee A. Negative pressure pulmonary oedema following use of ProSeal LMA. Indian J Anaesth. 2013;57(2):188-190. https://doi.org/10.4103/0019-5049.111854
10. Toukan Y, Gur M, Keshet D, Bentur L. Negative Pressure Pulmonary Edema in a Child Following Laryngospasm Triggered by a Laryngeal Mask. Isr Med Assoc J. 2019;21(1):56-57.

Denial of and disbelief in COVID-19

Rujittika Mungmunpuntipantip[1], Viroj Wiwanitkit[2,3]

TO THE EDITOR:

We would like to discuss a study called "Factors underlying denial of and disbelief in COVID-19," which looks into what influences or encourages doubt and unfavorable opinions concerning COVID-19.[1] In that study, the authors point out that a number of steps must be taken to promote vaccination and to reduce instances of denial and skepticism regarding COVID-19, and that governments should put in place a number of strategies to control the disease, while taking into consideration the psychological and social ramifications of those policies.[1]

In order to increase immunization rates and provide doubters with reliable information, it is essential to increase public confidence in authorities, experts, and scientists. For a variety of reasons, local COVID-19 control efforts may encounter support or opposition. The most noteworthy of those reasons is apprehension about vaccination, which has been linked to mistrust of the local health care system.[2] The willingness of a person to support public health initiatives depends on how much they trust their local public health response to a crisis.

How much a person trusts their local public health response to a crisis determines how ready they are to adhere to public health measures for disease epidemic management during the COVID-19 pandemic.[3] There is proof that people's attitudes toward vaccination vary based on their background and environment. People's decisions seem to change as their local environment changes. It is essential to comprehend the sad events that followed. To that end, the impacts of COVID-19 vaccination, local public health measures against COVID-19, and varying local epidemic stages should all be investigated using a longitudinal study design.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Vasilopoulos A, Pantelidaki NA, Tzoura A, Papadopoulou D, Stilliani K, Paralikas T, et al. Factors underlying denial of and disbelief in COVID-19. J Bras Pneumol. 2022;48(5):e20220228. https://doi.org/10.36416/1806-3756/e20220228
2. Sookaromdee P, Wiwanitkit V. Factors influencing COVID-19 vaccine acceptance and hesitancy: Correspondence. Hum Vaccin Immunother. 2022;2085471. https://doi.org/10.1080/21645515.2022.2085471
3. Mungmunpuntipantip R, Wiwanitkit V. COVID-19 vaccination hesitancy. Recenti Prog Med. 2021;112(9):596. https://doi.org/10.1701/3658.36425

1. Private Academic Consultant, Bangkok, Thailand.
2. Joseph Ayobabalola University, Ikeji-Arakeji, Nigeria.
3. Dr. DY Patil Medical College, Dr. DY Patil Vidyapeeth, Pune, India.

ISSN 1806-3756

Authors' reply

Aristidis Vasilopoulos[1], Nikoleta-Alexandra Pantelidaki[2], Aggeliki Tzoura[2], Dimitra Papadopoulou[2], Stilliani Kotrotsiou[3], Theodosios Paralikas[3], Eleni Kortianou[1], Dimos Mastrogiannis[4]

TO THE EDITOR:

We received the correspondence regarding our recently published article and we thank you. We read this well-written correspondence carefully and are glad that the authors are in agreement with our findings and conclusions.

As is widely acknowledged in the literature, there is not only one reason for disbelief or hesitancy toward COVID-19 or toward the available vaccines developed to protect humanity from this disease. Nevertheless, disbelief and hesitancy have been documented as a worldwide phenomenon affecting all countries.

Fortunately, according to Lazarus et al.,[1] COVID-19 vaccine acceptance increased over the last year in most of the 19 countries studied in 2020 and 2021. However, even though the reported level of acceptance rose to 75.2% in the 23 countries studied in 2021, it remains below the level required to tackle the pandemic successfully.[1]

Consequently, each country needs to investigate the reasons behind the disbelief in COVID-19 and the vaccine hesitancy and act accordingly, because the factors associated with this phenomenon vary considerably from country to country. Some of these factors include gender, age, income, health condition, and place of residence.[2]

Also, circulating misinformation had a negative impact on each national health care system's attempt to implement scientifically sound strategies to confront the COVID-19 pandemic. As a result of misinformation, people may become confused and hesitant, suspect vaccine efficacy, and, consequently, avoid vaccination. As has been suggested elsewhere,[3] we strongly believe that primary care needs to be supported and used as a pillar to inform people about and restore their trust in the health care systems and scientific achievements altogether.

Finally, we advocate that cooperation among nations and exchange of information, research findings, and good practices are essential to effectively control this pandemic.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Lazarus JV, Wyka K, White TM, Picchio CA, Rabin K, Ratzan SC, et al. Revisiting COVID-19 vaccine hesitancy around the world using data from 23 countries in 2021. Nat Commun. 2022;13(1):3801. https://doi.org/10.1038/s41467-022-31441-x
2. Stojanovic J, Boucher VG, Gagne M, Gupta S, Joyal-Desmarais K, Paduano S, et al. Global Trends and Correlates of COVID-19 Vaccination Hesitancy: Findings from the iCARE Study. Vaccines (Basel). 2021;9(6):661. https://doi.org/10.3390/vaccines9060661
3. Tharmaratnam T, D'Urzo A, Cazzola M. Medical knowledge about COVID-19 is travelling at the speed of mistrust: why this is relevant to primary care. Fam Pract. 2022;39(5):988-991. https://doi.org/10.1093/fampra/cmac001

1. Department of Physiotherapy, University of Thessaly, Lamia, Greece.
2. Undergraduate Program of Nursing, University of Thessaly, Lamia, Greece.
3. General Department, University of Thessaly, Larisa, Greece.
4. General Department, University of Thessaly, Lamia, Greece.

List of reviewers for volume 48 (1-6) 2022

Adrian Ceccato - Hospital Nacional Profesor Alejandro Posadas - Buenos Aires, Argentina
Alberto Cukier - Universidade de São Paulo - São Paulo - SP
Alberto Vergara - Hospital Infantil João Paulo II - Belo Horizonte, Brasil
Alcindo Cerci Neto - Universidade Estadual de Londrina Centro de Ciencias da Saude Clinica Médica - Londrina - PR
Aldo Agra de Albuquerque Neto - Universidade Federal de São Paulo - São Paulo - SP
Aleksandar Sovtic - The Institute for Health Protection of Mother and Child Serbia Belgrade, Serbia
Alessandro Heubel - UFSCar - Universidade Federal de São Carlos - São Carlos, SP, Brasil
Alessandro Mariani - Universidade de São Paulo - São Paulo - SP
Alexandre Amaral - Universidade de São Paulo - São Paulo - SP
Alexandre Dias Mançano - Hospital Anchieta - Taguatinga - DF
Alexandre Kawassaki - Universidade de São Paulo - São Paulo - SP
Alexandre Souza - Universidade Federal de São Paulo, São Paulo, Brazil
Alexandre Zavascki - UFRGS - Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
Alfredo Nicodemos Cruz Santana - HRAN da Faculdade de Medicina da ESCS - Brasília - DF
Aline Aielo - Universidade de São Paulo - São Paulo - SP
Ana Paula Santos - Fundação Oswaldo Cruz - Rio de Janeiro - RJ
Andre Nyberg - Department of Community Medicine and Rehabilitation, Section of Physiotherapy, Umeå University, Umeå, Sweden
Andrea Celtin - Universidade de São Paulo, São Paulo, Brazil.
Anna Carvalho -Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Antenor Rodrigues - Universidade Estadual de Londrina - Londrina, Brazil
Anton Kiselev - Ott's Institute for Obstetrics and Gynecology RAMS Saint-Petersburg Russia
Arthur Soares Souza Júnior - Faculdade de Medicina de São José do Rio Preto - São José do Rio Preto - SP
Benoit Bibas - Universidade de São Paulo - São Paulo - SP
Bruno Andrade - Fundacao Oswaldo Cruz Instituto Gonçalo Moniz - Salvador - Bahia
Bruno do Valle Pinheiro - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Bruno Guedes Baldi - Universidade de São Paulo - São Paulo - SP
Bruno Hochhegger - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Caio Morais - Universidade de São Paulo - São Paulo - SP
Carla Malaguti - Universidade Federal de Juiz de Fora - Juiz de Fora -MG
Carlos Ferreira - Oncoclinicas do Brasil Ensino e Pesquisa - Rio de Janeiro - RJ
Carmen Sílvia Valente Barbas - Universidade de São Paulo - São Paulo - SP
Caroline Fernandes-James - North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees - UK
Celso Carvalho - Universidade de São Paulo - São Paulo - SP
Cemile Bozdemir-Ozel - Eskisehir Osmangazi University - Eskisehir - Turkey
Christiano Perin - LabSono - Hospital Mãe de Deus - Porto Alegre -RS
Cristiano Andrade - Hospital de Clinicas de Porto Alegre - Porto Alegre - RS
Cristino Oliveira - Universidade Federal de Juiz de Fora – Juiz de Fora - MG
Daniel Winter - Universidade de Uberaba - Campus Aeroporto - Uberaba - MG
Daniele Cataneo - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Danielle Climaco - Hospital Otávio de Freitas - Recife - PE
Danilo Cortozi Berton - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Dante Escuissato - Universidade Federal do Paraná - Curitiba - PR
Débora Chong e Silva - Universidade Federal do Paraná - Curitiba - PR
Dejan Radovanovic - University of Milan Department of Biomedical and Clinical Sciences - Milano - Italy
Denilson Petrochi - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Denise Rossato Silva - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Diana Penha - Liverpool Heart and Chest Hospital - Liverpool - Reino Unido
Diego Poddighe - KU Leuven Department of Rehabilitation Sciences - Belgium
Eanes Barros Pereira - Universidade Federal do Ceará - Fortaleza - CE
Ebru Calik Kutukcu - Hacettepe University - Turkey
Edilson Zancanela - Universidade Estadual de Campinas - Campinas - SP
Edimar Gomes - Universidade Federal de Juiz de Fora - MG
Edson Marchiori - Universidade Federal Fluminense - Niterói - RJ
Eduardo Algranti - Fundação Jorge Duprat Figueiredo de Segurança e Medicina do Trabalho - São Paulo - SP
Eduardo De Capitani - Universidade Estadual de Campinas - Campinas - SP
Eduardo Fonseca - Universidade de São Paulo - São Paulo - SP
Eduardo Saito - Universidade do Estado do Rio de Janeiro - Rio de Janeiro - RJ
Eduardo Werebe - Hospital Israelita Albert Einstein - São Paulo - SP
Ekaterini Goudouris - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Elenara Procianoy - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Eliseo Eugenin - University of Texas Medical Branch - Galveston - United States
Eliseu Waldman - Universidade de São Paulo - São Paulo - SP
Eloara Vieira Machado Ferreira - Universidade Federal de São Paulo - São Paulo - SP
Erich Carvalho - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Eserval Rocha Junior - Hospital Israelita Albert Einstein - São Paulo - SP
Fabiano Di Marco - University of Milan - Italy
Fabio Haddad - Hospital A.C.Camargo Cancer Center - São Paulo - SP

ISSN 1806-3756

Fabio Minamoto - Universidade de São Paulo - São Paulo - SP
Fábio Muchão - Universidade de São Paulo - São Paulo - SP
Fábio Pitta - Universidade Estadual de Londrina - Londrina - PR
Fabio Silva - Universidade Federal da Paraíba - Joao Pessoa - PB
Federico Garcia Cipriano - Universidade de São Paulo - São Paulo - SP
Felipe von Ranke - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Felippe Dexheimer Neto - Moinhos de Vento Hospital - Porto Alegre - RS
Fernanda Carvalho de Queiroz Mello - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Fernando Lundgren - Hospital Otávio de Freitas - Recife - PE
Flávio Arbex - Universidade Federal de São Paulo - São Paulo - SP
Frederico Friedrich - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Frederico Leon Arrabal Fernandes - Universidade de São Paulo - São Paulo - SP
Gilberto Castro Junior - Instituto Brasileiro de Controle do Câncer - São Paulo- SP
Gonzalo Labarca - Complejo Asistencial Víctor Ríos Ruiz Internal Medicine - Chile
Gustavo Chatkin - - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Gustavo Schvartsman - Hospital Israelita Albert Einstein - São Paulo - SP
Gustavo Zabert - Universidad Nacional del Comahue Medicina y Cirugia - Argentina
Hugo Yoo - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Hye Yun Park - Hanyang University - Seoul - Korea.
Irma de Godoy - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Jordi Rello - Universitat Internacional de Catalunya - Barcelona - Spain
José Ângelo Rizzo - Universidade Federal de Pernambuco - Recife - PE
José Antônio Baddini Martinez - Universidade Federal de São Paulo - São Paulo - SP
José Dirceu Ribeiro - Universidade Estadual de Campinas - Campinas - SP
José Roberto Jardim - Universidade Federal de São Paulo - São Paulo - SP
Juliano Arcuri - Universidade Federal de São Carlos - São Paulo - SP
Julio Croda - Universidade Federal da Grande Dourados - Mato Grosso - Brasil
Julio Rodrigues Filho - Universidade Federal do Estado do Rio de Janeiro - Rio de Janeiro - RJ
Kaifeng Xu - Mayo Clinic - Division of Pulmonary and Critical Care Medicine, USA.
Klaus Irion - School of Biological Sciences, The University of Manchester, United Kingdom
Laura Cabral - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Laura Neves - Universidade Federal do Pará - Belém - PA
Leandro Fritscher - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Leonardo Araújo Pinto - Pontifícia Universidade Católica do Grande do Sul - Porto Alegre - RS
Leonardo Staub - Universidade Federal de Santa Catarina - Santa Catarina - SC
Leticia Cardenas - Universidade de São Paulo - São Paulo -SP
Leticia Kawano-Dourado - Universidade de São Paulo - São Paulo - SP
Lia Possuelo - Universidade de Santa Cruz do Sul - Santa Cruz - Rio Grande do Sul - RS
Liana Coelho - Universidade Estadual Paulista "Julio de Mesquita Filho" - Botucatu - SP
Liana Kortianou - University of Thessaly Physiotherapy - Greece
Lídia Fonseca - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Lilian Caetano - Universidade Federal de São Paulo, São Paulo, SP
Liliane Mendes - Universidade Federal de Minas Gerais - Belo Horizonte - MG
Luca Novelli - Careggi University Hospital – Firenze - Italy
Luciana Chiavegato - Universidade Cidade de São Paulo - São Paulo – SP
Lucyara Catunda - Hospital Universitário Walter Cantídio - Fortaleza - Ceará
Luis Carlos Maia Cardozo Junior - Universidade de São Paulo - São Paulo - SP
Luis Coelho - Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal.
Luiz Paulo Loivos - Hospital Universitário Clementino Fraga Filho - Rio de Janeiro - Brasil.
Luiz Vicente da Silva Filho - Universidade de São Paulo - São Paulo - SP
Manoel Ribeiro - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Marcela Muñoz-Torrico - National Institute of Respiratory Diseases of Mexico
Marcelo Basso Gazzana - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Marcelo Fuccio - Fundação Hospitalar do Estado de Minas Gerais - MG
Marcelo Gazzana - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Marcelo Gregório - Hospital Israelita Albert Einstein Morumbi - São Paulo - SP
Marcelo Holanda - Universidade Federal do Ceará - Ceará - CE
Marcelo Litvoc - Universidade de São Paulo - São Paulo -SP
Marcelo Rabahi - Universidade Federal de Goiás - Goiania - GO
Marcelo Rocha - Centro Universitario Christus - Fortaleza - Ceará
Marcelo Velloso - Universidade Federal de Minas Gerais - Belo Horizonte - MG
Márcia Barbosa - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Marcia Jacomelli - Universidade de São Paulo - São Paulo -SP
Márcia Margaret Menezes Pizzichini - Universidade Federal de Santa Catarina - Florianópolis – SC
Marcio Donadio - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Márcio Sawamura - Universidade de São Paulo - São Paulo - SP
Marco Contoli - University of Ferrara Translational Medicine - Italy
Marcos Minicucci - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Maria Angélica Ferreira - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Mariana Hoffman - Monash University Department of Allergy, Immunology and Respiratory Medicine - Australia
Mariana Lima - Hospital do Servidor Público Estadual de São Paulo Pneumologia - São Paulo - SP
Marianna Mantzorou - University of West Attica Nursing Agiou Spiridonos, Aigaleo Athens - Greece
Matheus Zanon - Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre - RS
Matteo Baldisserotto - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Maurício Saueressig - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Mayara Cabrini - Universidade de São Paulo - São Paulo - SP

Maycon Reboredo - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Mayra Pereira - Universidade de São Paulo - São Paulo - SP
Monica Firmida - Universidade do Estado do Rio de Janeiro - Rio de Janeiro - RJ
Mônica Pereira - Universidade Estadual de Campinas - Campinas - SP
Natália Campos - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Neilane Bertoni - Instituto Nacional do Câncer - Rio de Janeiro - RJ
Nicolau Guerreiro - Hospital Sírio-Libanês - São Paulo - SP
Otávio Tavares Ranzani - Barcelona Global Health Institute - ISGlobal, Barcelona, Espanha
Patricia Tuma - Hospital Israelita Albert Einstein - São Paulo - SP
Paula Gaiolla - Universidade de São Paulo - São Paulo - SP
Pauliane Santana - Universidade de São Paulo - São Paulo - SP
Paulo Camargos - Universidade Federal de Minas Gerais – Belo Horizonte - BH
Paulo de Tarso Dalcin - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Paulo Scordamaglio - Hospital Israelita Albert Einstein Morumbi - São Paulo - SP
Pedro Araújo - Universidade de São Paulo - São Paulo - SP
Pedro Leme - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Pedro Paulo Torres - Multimagem Diagnósticos - Goiânia - GO
Pedro Reck dos Santos - University of Pittsburgh - Pennsylvania - United States
Pedro Rodrigues Genta - Universidade de São Paulo - São Paulo - SP
Pilar Cebollero - Hospital de Navarra - Spain
Priscila Cilene Camargo - Universidade de São Paulo - São Paulo - SP
Rafael Grando - Hospital Moinhos de Vento - Porto Alegre - RS
Rafael Mesquita - Universidade Federal do Ceará - CE
Renata Ferrari - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Renata Fumis - Hospital Sírio-Libanês - São Paulo - SP
Ricardo Bammann - Instituto de Infectologia Emílio Ribas - São Paulo - SP
Ricardo Figueiredo - Universidade Estadual de Feira de Santana - Bahia - BA
Ricardo Mingarini Terra - Universidade de São Paulo - São Paulo - SP
Rita Mattiello - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Roberta Carvalho - Universidade Federal Fluminense – Niterói - RJ
Roberto Rodrigues Júnior - Faculdade de Medicina do ABC - Santo André - SP
Rodrigo A. Athanazio - Universidade de São Paulo - São Paulo - SP
Rogelio Pérez-Padilla - Instituto Nacional de Enfermedades Respiratorias - México
Roger Calderon - Laboratorio Socios En Salud Sucursal Perú - Perú
Rogerio Souza - Universidade de São Paulo - São Paulo - SP
Rosemeri Maurici - Universidade Federal de Santa Catarina - Florianópolis - SC
Rudolf Oliveira - Universidade Federal de São Paulo - São Paulo -SP
Rui Haddad - Pontifícia Universidade Católica do Rio de Janeiro - Rio de Janeiro - RJ
Santiago Arce - Medical Research Institute Alfredo Lanari - Argentina
Sauwaluk Dacha - Faculty of Associated Medical Sciences, Chiang Mai University - Thailand
Sérgio Amantea - Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre - RS
Sergio Paiva - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Silvana Miranda - Universidade Federal de Minas Gerais - Minas Gerais - MG
Silvia Rodrigues - Instituto de Assistência Médica ao Servidor Público Estadual - São Paulo - SP
Silvia Terraneo - University of Milan - Milan - Italy
Simone Dal Corso - Universidade Nove de Julho - São Paulo - SP
Simone Fagondes - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Sotirios Plakas - Department of Nursing University of West Attica - Greece
Stella Martins - Universidade de São Paulo - São Paulo - SP
Stephan Altmayer - Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre - RS
Suzana Erico Tanni - Universidade Estadual Paulista "Julio de Mesquita Filho" - Botucatu - SP
Teresa Takagaki - Universidade de São Paulo - São Paulo - SP
Thaís Sant'Anna - Universidade Federal do Amazonas - Manaus - AM
Thiago Bártholo - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Ubiratan de Paula Santos - Universidade de São Paulo - São Paulo - SP
Valéria Di Lorenzo - Universidade Federal de São Carlos - São Paulo - SP
Valéria Maria Augusto - Universidade Federal de Minas Gerais - Belo Horizonte - MG
Vania Nogueira - Department of Biochemistry and Molecular Genetics - Chicago
Veronica Moreira Amado - Universidade de Brasília - Brasília - DF
Victor Ribeiro Neves - Universidade Federal de Pernambuco – Recife - PE
Vitor Codeço - Universidade de Brasília - Brasília - DF
Vladimir Lima - Universidade de São Paulo - São Paulo - SP
Wagner Diniz - Hospital Universitário de Brasília - Brasiília - DF
Wei-Cheng Tseng - Tri-Service General Hospital – Taiwan
Zafeiris Louvaris - University Hospitals Leuven - Leuven - Belgium

The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3756, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

After being approved by the Editorial Board, all articles will be evaluated by qualified reviewers, and anonymity will be preserved throughout the review process.

Articles that fail to present merit, have significant errors in methodology or are not in accordance with the editorial policy of the journal will be directly rejected by the Editorial Board, with no recourse. Articles may be written in Portuguese, Spanish or English. In the online version of the Journal (www.jornaldepneumologia.com.br, ISSN-1806-3756), all articles will be made available in Spanish or Portuguese, as well as in English. Authors may submit color figures. However, the cost of printing figures in color, as well as any related costs, will be borne by the authors.

For further clarification, please contact the Journal Secretary by e-mail or by telephone.

The *Jornal Brasileiro de Pneumologia* upholds the World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE) policies regarding the registration of clinical trials, recognizing the importance of these initiatives for the registration and international, open-access dissemination of information on clinical trials. Therefore, as of 2007, the Journal only accepts clinical trials that have been given an identification number by one of the clinical trials registries meeting the criteria established by the WHO and the ICMJE. This identification number must be included at the end of the abstract.

Within this context, the *Jornal Brasileiro de Pneumologia* adheres to the definition of a clinical trial as described by the WHO, which can be summarized as "any study that prospectively assigns human beings to be submitted to one or more interventions with the objective of evaluation the effects that those interventions have on health-related outcomes. Such interventions include the administration of drugs, cells and other biological products, as well as surgical procedures, radiological techniques, the use of devices, behavioral therapy, changes in treatment processes, preventive care, etc

Authorship criteria

An individual may be considered an author of an article submitted for publication only if having made a significant intellectual contribution to its execution. It is implicit that the author has participated in at least one of the following phases: 1) conception and planning of the study, as well as the interpretation of the findings; 2) writing or revision of all preliminary drafts, or both, as well as the final revision; and 3) approval of the final version.

Simple data collection or cataloging does not constitute authorship. Likewise, authorship should not be conferred upon technicians performing routine tasks, referring physicians, doctors who interpret routine exams or department heads who are not directly involved in the research. The contributions made by such individuals may be recognized in the acknowledgements.

The accuracy of all concepts presented in the manuscript is the exclusive responsibility of the authors. The number of authors should be limited to eight, although exceptions will be made for manuscripts that are considered exceptionally complex. For manuscripts with more than six authors, a letter should be sent to the Journal describing the participation of each.

Presentation and submission of manuscripts

All manuscripts must be submitted online from the home-page of the journal. The instructions for submission are available at: www.jornaldepneumologia.com.br/sgp. Although all manuscripts are submitted online, they must be accompanied by a Copyright Transfer Statement and Conflict of Interest Statement signed by all the authors based on the models available at: www.jornaldepneumologia.com.br.

It is requested that the authors strictly follow the editorial guidelines of the journal, particularly those regarding the maximum number of words, tables and figures permitted, as well as the rules for producing the bibliography. Failure to comply with the author instructions will result in the manuscript being returned to the authors so that the pertinent corrections can be made before it is submitted to the reviewers.

Special instructions apply to the preparation of Special Supplements and Guidelines, and authors should consult the instructions in advance by visiting the homepage of the journal.

The journal reserves the right to make stylistic, grammatical and other alterations to the manuscript.

With the exception of units of measure, abbreviations should be used sparingly and should be limited only to those that are widely accepted. These terms are defined in the List of Abbreviations and Acronyms accepted without definition in the Journal. Click here (List of Abbreviations and Acronyms). All other abbreviations should be defined at their first use. For example, use "C-reactive protein (CRP)", and use "CRP" thereafter. After the definition of an abbreviation, the full term should not appear again. Other than those accepted without definition, abbreviations should not be used in titles, and their use in the abstracts of manuscripts should be avoided if possible.

Whenever the authors mention any substance or uncommon piece of equipment they must include the catalogue model/number, name of manufacturer, city and country of origin. For example:

"... ergometric treadmill (model ESD-01; FUNBEC, São Paulo, Brazil) ..."

In the case of products from the USA or Canada, the name of the state or province should also be cited. For example:

"... guinea pig liver tTg (T5398; Sigma, St. Louis, MO, USA) ..."

Manuscript preparation

Title Page: The title page should include the title (in Portuguese and in English); the full names, highest academic degrees and institutional affiliations of all authors; complete address, including telephone number, fax number and e-mail address, of the principal author; and a declaration of any and all sources of funding.

Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles may be unstructured.

Abstracts for brief communications should not exceed 100 words.

Summary: An abstract in English, corresponding in content to the abstract in Portuguese, should be included.

Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the

corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

Text:

Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

Review and Update articles: Review and Update articles are written at the request of the Editorial Board, which may occasionally accept unsolicited manuscripts that are deemed to be of great interest. The text should not exceed 5000 words, excluding references and illustrations (figures or tables). The total number of illustrations should not exceed eight. The number of references should not exceed 60.

Pictorial essays: Pictorial essays are also submitted only at the request of the Editors or after the authors have consulted and been granted permission by the Editorial Board. The text accompanying such essays should not exceed 3000 words, excluding the references and tables. No more than 12 illustrations (figures and tables) may be used, and the number of references may not exceed 30.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

Correspondence: Authors may submit comments and suggestions related to material previously published in our journal. Such submissions should not exceed 500 words.

Imaging in Pulmonary Medicine: Submissions should not exceed 200 words, including the title, text, and references (no more than three). Authors may include up to three figures, bearing in mind that the entire content will be published on a single page.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

All correspondence to the Jornal Brasileiro de Pneumologia should be addressed to:

Prof. Dr. Rogério Souza

Editor-Chefe do Jornal Brasileiro de Pneumologia

SCS Quadra 01, Bloco K, Salas 203/204 - Ed. Denasa. CEP: 70.398-900 - Brasília - DF, Brazil

Telefones/Fax: 0xx61-3245-1030, 0xx61-3245-6218

Jornal Brasileiro de Pneumologia e-mail address:

jpneumo@jornaldepneumologia.com.br

(Assistente Editorial - Luana Campos)

Online submission of articles:

www.jornaldepneumologia.com.br

Eventos SBPT 2023

XI Curso Nacional de Doenças Intersticiais
Data: 17 e 18 de março
Local: Centro de Convenções Rebouças, São Paulo/SP
Inscrições: Em breve

Oficina de Acolhimeto – SBPT ACOLHE
Data: 15 e 16 de abril
Local: Faculdade de Medicina da Universidade de São Paulo (FMUSP)
Inscrições: Em breve

XXII Curso Nacional de Atualização em Pneumologia
IV Curso Nacional de Atualização em Pneumologia Pediátrica
Data: 20 a 22 de abril
Local: Rio Othon Palace - Rio de Janeiro/RJ
Inscrições: Em breve

Asma 2023
XII Congresso Brasileiro de Asma
IX Congressos Brasileiros de DPOC e Tabagismo
II Congresso Paranaense de Pneumologia e Tisiologia
Data: 02 a 05/08/2023
Local: Curitiba/PR
Inscrições: Em breve

Eventos SBPT 2024

Congresso 2024
41° Congresso Brasileiro de Pneumologia e Tisiologia
17° congresso Brasileiro de Endoscopia Respiratória
Data: 09 a 12/10/2024
Local: Florianópolis/SC

Estaduais da Sociedade Brasileira de Pneumologia e Tisiologia

ASSOCIAÇÃO ALAGOANA DE DOENÇAS DO TÓRAX - AADT
Presidente: Fernando Antônio Mendonça Guimarães
Secretária: Othenilze Duran de Araújo
Endereço: Rua Professor José Silveira Camerino, nº 1085/ Sala 501, Pinheiro,
CEP: 57.057-250 - Maceió – AL
Telefone: (82) 99317-8574
Email: sociedadealagoana.dt@gmail.com
famguima@gmail.com

ASSOCIAÇÃO AMAZONENSE DE PNEUMOLOGIA E CIRURGIA TORÁCICA
Presidente: Mário Sergio Monteiro Fonseca
Secretária: Tatiana Minda Herculano Cattebeke
Endereço: Av. Eduardo Ribeiro, nº 520, 12º andar, Sala 1204, Edifício Manaus SH Centro - Centro
CEP: 69.020-030 - Manaus – AM
Telefone: (92) 2101-2586, (92) 98120-4400
E-mail: aapctmanaus@gmail.com
ms-fonseca@uol.com.br

ASSOCIAÇÃO CATARINENSE DE PNEUMOLOGIA E TISIOLOGIA - ACAPTI
Presidente: Roger Pirath Rodrigues
Secretário: Márcio Andrade Martins
Endereço: Rodovia SC, 401 Km 4 – 3854 - Saco Grande
CEP: 88.032-005 - Florianópolis – SC
Telefone: (48) 32310314
E-mail: acapti@acapti.org.br
Site: www.acapti.org.br

ASSOCIAÇÃO DE PNEUMOLOGIA E CIRUGIA TORÁCICA DO RIO GRANDE DO NORTE
Presidente: Suzianne Ruth Hosannah de Lima Pinto
Secretária: Soraia Bernardo Monteiro Cardoso
Endereço: Av. Campos Sales, 762 - Tirol
CEP: 59.020-300 - Natal – RN
Telefone: (84) 99169.9973
E-mail: suzirh@gamil.com | rnapct@gmail.com

ASSOCIAÇÃO MARANHENSE DE PNEUMOLOGIA E CIRURGIA TORÁCICA
Presidente: Maria do Rosario da Silva Ramos Costa
Secretário: João Batista de Sá Filho
Endereço: Travessa do Pimenta, 46 - Olho D'Água
CEP: 65.065-340 - São Luís – MA
Telefone: (98) 32486379/21091295 - (98)999736600
E-mail: rrcosta2904@gmail.com

ASSOCIAÇÃO PARAENSE DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Lúcia Helena Messias Sales
Secretária: Tainã Tavares Brito de Aguiar
Endereço: Travessa Dom Romualdo de Seixas, 1529 - Sala 06 - Umarizal
CEP: 66050-200 - Belém – PA
Telefone: (91) 32222224)
E-mail: spapnt@gmail.com | lhsales@ufpa.br

ASSOCIAÇÃO PARANAENSE DE PNEUMOLOGIA E TISIOLOGIA (APPT)
Presidente: Leda Maria Rabelo
Secretário: Orjana Araújo de Freitas
Endereço: Av. Sete de Setembro, 5402 - Conj. 105, 10ª andar Batel
CEP: 80240-000 - Curitiba – PR
Tel/fax: (41) 3342-8889
E-mail: contato@pneumopr.org.br
Site: www.pneumopr.org.br

ASSOCIAÇÃO PERNAMBUCANA DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Adriana Velozo Gonçalves
Secretária: Danielle Cristina Silva Clímaco
Endereço: Rua João Eugênio de Lima , 235 - Boa Viagem
CEP: 51030-360 - Recife – PE
Tel/fax: (81) 988817435
E-mail: pneumopernambuco@gmail.com
adrianavelozo@hotmail.com

ASSOCIAÇÃO PIAUIENSE DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Braulio Dyego Martins Vieira
Secretária: Tatiana Santos Malheiros Nunes
Endereço: Avenida Jose dos Santos e Silva, 1903, Nucleo de Cirurgia Torácica
CEP: 64001-300 - Teresina – PI
Telefone: (86) 32215068 - (86) 999306664
E-mail: brauliodyego@gmail.com

SOCIEDADE BRASILIENSE DE DOENÇAS TORÁCICAS
Presidente: Nathali Mireise Costa Ferreira
Secretária: Milena Zamian Danilow
Endereço: Setor de Clubes Sul, Trecho 3, Conj. 6
CEP: 70.200-003 - Brasília – DF
Tel/fax: (61) 3245-8001
E-mail: sbdt@ambr.org.br

SOCIEDADE CEARENSE DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Ricardo Coelho Reis
Secretário: Ivan Guerra De Araújo Freitas
Endereço: Av. Dom Luis, 300, sala 1122, Aldeota
CEP: 60.160-230 - Fortaleza – CE
Telefone: (85) 3092-0401/3264-9466
E-mail: assessoria@scpt.org.br; amc@amc.med.br
Site: www.scpt.org.br

SOCIEDADE DE PNEUMOLOGIA DA BAHIA
Presidente: Jorge Luiz Pereira e Silva
Secretário: César Augusto de Araújo Neto
Endereço: ABM - Rua Baependi,162 Sala 03 - Terreo- Ondina
CEP: 40.170-070 - Salvador – BA
Tel/fax: (71) 33326844
E-mail: pneumoba@gmail.com | spba@outlook.com.br

SOCIEDADE DE PNEUMOLOGIA DO ESPÍRITO SANTO - SPES
Presidente: Rafael de Castro Martins
Secretária: Karina Tavares Oliveira
Endereço: Rua Eurico de Aguiar, 130, Sala 514, Ed. Blue Chip, Praia do Campo
CEP: 29.055-280 - Vitória – ES
Telefone: (27) 3345-0564 - (27) 999826598
E-mail: rafaelcastromartins@gmail.com

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO MATO GROSSO - SPMT
Presidente Clovis Botelho
Secretária: Wandoircy Silva Costa
Endereço: Av. Miguel Sutil, n 8000, Edf. Santa Rosa Tower, sala 602 – Vila Mariana
CEP: 78.040-790 - Cuiabá – MT
Telefone: (65) 996581548
E-mail: clovisbotelho8@gmail.com

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO MATO GROSSO DO SUL
Presidente: Henrique Ferreira de Brito
Secretário: Luiz Armando Pereira Patusco
Endereço: Rua 15 de novembro,2552, Ed. One Offices, Sala 901
CEP: 79.020-300 - Campo Grande - MS
Telefone: (67)981628382 – (67)33274110
E-mail: especialidades@amms.com.br

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO ESTADO DO RIO DE JANEIRO
Presidente: Fernanda de Carvalho de Queiroz Mello
Secretário: Ricardo Luiz de Menezes Duarte
Endereço: Largo do Machado, 21, GR. 08, sala 914, Catete
CEP: 22.221-020 - Rio de Janeiro – RJ
Tel/fax: (21) 3852-3677
E-mail: sopterj@sopterj.com.br
Site: www.sopterj.com.br

SOCIEDADE DE PNEUMOLOGIA E TISIOLOGIA DO RIO GRANDE DO SUL
Presidente: Gustavo Chatkin
Vice Presidente: Paulo Roberto Goldenfum
Endereço: Av. Ipiranga, 5.311, sala 403
CEP: 90.610-001 - Porto Alegre – RS
Telefone: (51) 3384-2889
E-mail: sptrs.secretaria@gmail.com
Site: www.sptrs.org.br

SOCIEDADE GOIANA DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Karla Cristina de Moraes Arantes Curado
Secretária: Roseliane de Souza Araújo
Endereço: Galeria Pátio 22, Rua 22 nº 69, Sala 17, Setor Oeste
CEP: 74.120-130 - Goiânia – GO
Telefone: (62) 3251-1202 / (62) 3214-1010
E-mail: sgpt2007@gmail.com | karlacurado1@hotmail.com

SOCIEDADE MINEIRA DE PNEUMOLOGIA E CIRURGIA TORÁCICA
Presidente: Marcelo Bicalho de Fuccio
Secretário: Luciana Macedo Guedes
Endereço: Av. João Pinheiro, 161 - sala 203 - Centro
CEP: 30.130-180 - Belo Horizonte – MG
Tel/fax: (31) 3213-3197
E-mail: smpct@smpct.org.br
Site: www.smpct.org.br

SOCIEDADE PARAIBANA DE TISIOLOGIA E PNEUMOLOGIA
Presidente: Maria Enedina Claudino Aquino Scuarcialupi
Secretária: Gerlânia Simplício Sousa
Endereço: Rua José Florentino Jr. 333– Tambauzinho
CEP: 58042-040 – João Pessoa – PB
Telefone: (83) 38863700
E-mail: enedinapneumo@enedinapneumo.com

SOCIEDADE PAULISTA DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Frederico Leon Arrabal Fernandes
Secretário: Rodrigo Abensur Athanazio
Endereço: Rua Machado Bittencourt, 205, 8° andar, conj. 83 - Vila Clementino
CEP: 04.044-000 São Paulo – SP
Telefone: 0800 17 1618
E-mail: sppt@sppt.org.br
Site: www.sppt.org.br

SOCIEDADE SERGIPANA DE PNEUMOLOGIA E TISIOLOGIA
Presidente: Edson Franco Filho
Secretário: Almiro Alves de Oliva Sobrinho
Endereço: Av. Gonçalo Prado Rollemberg, 211, Sala 206-Centro Médico - Bairro São José
CEP: 49.050-370 - Aracaju - SE
Telefone: (79) 999814482
E-mail: edac@uol.com.br

CONHEÇA O NOVO APLICATIVO DA BAYER!

O aplicativo **Risco na HP** facilita a utilização das estratégias para estratificação de risco do seu paciente, de acordo com as diretrizes do **Registro Francês**[1, 2], **Registro COMPERA**[3,4], **REVEAL 2.0 e REVEAL Lite 2**

O aplicativo Risco na HP está disponível para download gratuito nas principais lojas de aplicativo.

Baixar na App Store

DISPONÍVEL NO Google Play

O aplicativo Risco na HP foi desenvolvido com base em publicações científicas1-6 para realizar uma estimativa na estratificação de risco da Hipertensão Pulmonar.

A responsabilidade pela determinação da conduta terapêutica para cada paciente é do médico e sua equipe. O aplicativo apenas facilita a utilização das estratégias de avaliação de risco. As informações apresentadas pelo aplicativo não devem ser utilizadas isoladamente.

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.

PP-VEN-BR-0037-1 | Fevereiro 2022

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

Egurinel® (pirfenidona) é bioequivalente ao medicamento referência![1]

Referência: 1. Vespasiano CFP, Accennato VAC, Costa F, Riccio MF, Bernasconi G, et al. (2020) Bioequivalence between Two Capsules of Pirfenidona in Healthy Subjects under Fed Condition. J Bioeq Stud 6(1): 101.

EGURINEL® (pirfenidona) é apresentado em embalagem contendo 270 cápsulas. **Indicações**: EGURINEL® (pirfenidona) está indicado para tratamento de fibrose pulmonar idiopática (FPI). **Posologia**: Adultos: Ao iniciar o tratamento, a dose deve ser escalonada em um período de 14 dias até a dose diária recomendada de nove cápsulas por dia, como se segue: **Dias 1 a 7**: uma cápsula, três vezes por dia (801 mg/dia). **Dias 8 a 14**: duas cápsulas, três vezes por dia (1602 mg/dia). **Dias 15 em diante**: três cápsulas, três vezes por dia (2403 mg/dia). A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. 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® .

Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

30 ANOS Zodiac Produtos Farmacêuticos | ZODIAC